APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 FOR U.S. PATENT 4,572,912

Applicant	:	**Sankyo Co. Ltd.**
Patent Issue Date	:	**February 25, 1986**
Application Serial No.	:	**06/644,996**
Application Filing Date	:	**August 28, 1984**
Inventors	:	**Takao YOSHIOKA, Eiici KITAZAWA, Tomoyuki KURUMADA, Mitsuo YAMAZAKI and Kazuo HASEGAWA**
For	:	**THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM**

Attorneys for Applicant	:	***Frishauf, Holtz, Goodman, Langer & Chick, P.C.***
Attorney Docket	:	***84566/HG***

* * *

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

DECLARATION of Akio Nakamura,
dated February 17, 1997, on behalf
of the Applicant, Sankyo Co., Ltd.

LETTER OF LICENSEE by
Charles W. Ashbrook, Esq.,
dated January 31, 1997

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 USC 156

EXHIBITS

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 USC 156

TABLE OF CONTENTS

TABLE OF EXHIBITS

TRANSMITTAL

Attorney Docket No. 84566/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Sankyo Co. Ltd.
U.S. Patent No.:		4,572,912
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For	:	THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM
Attorneys for Applicant	:	Frishauf, Holtz, Goodman, Langer & Chick, P.C.

TRANSMITTAL OF AN APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (including an original and a certified duplicate original and attachments thereto, with a DECLARATION, signed by an officer of the Applicant, and with a LETTER OF THE LICENSEE, dated January 31, 1997, signed by Charles W. Ashbrook, Esq., Assistant General Counsel of the licensee) of the above-captioned patent for a product approved on January 29, 1997.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

[X] Enclosed is a check for the prescribed fee in the amount of $1,090.00 for the application presented.

In the event the actual fee differs from the check enclosed herewith, it is requested that the overpayment or underpayment be credited or charged to Deposit Account No. 06-1378.

Respectfully submitted,

Date: 26 Feb. 1997

HERBERT GOODMAN
REG. NO. 17,081

FRISHAUF, HOLTZ, GOODMAN,
LANGER & CHICK, P.C.
767 THIRD AVENUE - 25TH FLOOR
NEW YORK, NEW YORK 10017-2023
Tel. No. (212) 319-4900
Fax No. (212) 319-5101
HG/ma

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 and attachments thereto, with a DECLARATION and a LETTER OF THE LICENSEE

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM and attachments thereto, with the DECLARATION and the LETTER OF THE LICENSEE

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM and attachments thereto, with the DECLARATION and the LETTER OF THE LICENSEE

Attorney Docket No. 84566/HG U.S. Patent No. 4,572,912

Certified Duplicate

The undersigned hereby certifies that the attached APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 for U.S. Patent 4,572,912 and Exhibits are true copies of the original Application for Extension of Patent Term and Exhibits.

HERBERT GOODMAN
REG. NO. 17,081

DECLARATION

Attorney Docket No. 84566/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Sankyo Co. Ltd.

U.S. Patent No.: 4,572,912

Issue Date : February 25, 1986

Application Serial No. : 06/644,996

Application Filing Date : August 28, 1984

Inventors : Takao YOSHIOKA, Eiici KITAZAWA, Tomoyuki KURUMADA, Mitsuo YAMAZAKI and Kazuo HASEGAWA

For : THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

Attorneys for Applicant : Frishauf, Holtz, Goodman, Langer & Chick, P.C.

DECLARATION

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

I, Akio Nakamura, am an officer of Sankyo Co., Ltd., and have general authority from Sankyo Co., Ltd., to act on its behalf in patent matters, and declare as follows:

1. Sankyo Co., Ltd., is a corporation of Japan, having a place of business at 5-1, Nihonbashi Honcho, 3-chome, Chuo-ku, Tokyo 103, Japan (hereinafter referred to as "Sankyo").

Sankyo is the owner of United States Patent No. 4,572,912 by an assignment recorded in the United States Patent and Trademark Office on August 28, 1994, at Reel 4313, Frames 986 and 987.

2. In my capacity as an officer of Sankyo, I have reviewed

and understand the contents of the Application for Extension of Patent Term for United States Patent No. 4,572,912 submitted herewith pursuant to 35 USC 156.

3. I believe that the above-identified patent is subject to an extension pursuant to 37 CFR 1.710.

4. I believe that a 1534 day extension of the term of the patent is fully justified under 35 USC 156 and the applicable regulations.

5. I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made re punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application for extension of patent term and United States Patent No. 4,572,912.

Akio Nakamura

Name Akio Nakamura

Director, Patent Department

Corporate Title

Tokyo, Japan, February 17, 1997

Place Date

LICENSEE LETTER

Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105

Legal Division
(313) 996-7000
Telex: 297751 (WLPD UR)
Telecopy: 313-996-1553

WARNER LAMBERT

Charles W. Ashbrook
Telephone: (313) 996-5215

January 31, 1997

Via Federal Express

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: Application for Term Extension of
U.S. Patent No. 4,572,912

Sir:

I, Charles W. Ashbrook, as Assistant General Counsel of Pharmaceutical Patents for Warner-Lambert Company, having general authority from Warner-Lambert Company to act on its behalf in patent matters, state as follows:

1. Warner-Lambert Company, specifically its Parke-Davis Pharmaceutical Research Division, has a place of business at 2800 Plymouth Road, Ann Arbor, Michigan 48105.

2. Warner-Lambert Company is a licensee of U.S. Patent No. 4,572, 912, pursuant to a license agreement with Sankyo Co. Ltd., the record owner of U.S. Patent No. 4,572,912.

3. U.S. Patent No. 4,572,912 covers a compound known as troglitazone, the active ingredient in REZULIN™ and PRELAY™.

4. Parke-Davis Pharmaceutical Research Division and Warner-Lambert Company participated in the clinical evaluation and registration of REZULIN™ and PRELAY™, pursuant to NDA 20-720 which is owned by Warner-Lambert Company.

5. Warner-Lambert Company hereby authorizes Sankyo Co. Ltd., to rely on the activities of Warner-Lambert Company and its Parke-Davis Pharmaceutical Research Division pursuant to NDA 20-720 to file an application under 35 U.S.C. § 156 for extension of the term of U.S. Patent No. 4,572,912.

Very truly yours,

Charles W. Ashbrook

Charles W. Ashbrook
Assistant General Counsel, Pharmaceutical Patents

APPLICATION

HL-1090 Cleryl
DA/C for Patents

Attorney Docket No. 84566/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Sankyo Co. Ltd.

U.S. Patent No.: 4,572,912

Issue Date : February 25, 1986

Application Serial No. : 06/644,996

Application Filing Date : August 28, 1984

Inventors : Takao YOSHIOKA, Eiici KITAZAWA, Tomoyuki KURUMADA, Mitsuo YAMAZAKI and Kazuo HASEGAWA

For : THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

Attorneys for Applicant : Frishauf, Holtz, Goodman, Langer & Chick, P.C.

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Pursuant to 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the provisions of 35 USC 156, Sankyo Co., Ltd., a corporation of Japan, having a place of business at 5-1, Nihonbashi Honcho, 3-chome, Chuo-ku, Tokyo 103, Japan (hereinafter referred to as "Sankyo" or "Applicant"), the assignee of record of United States Patent No. 4,572,912, hereby applies for an extension of 1534 days of the term of United States Patent No. 4,572,912, issued February 25, 1986 on patent application Serial No. 06/644,996 filed August 28, 1984.

The following information is submitted in accordance with 35 USC § 156(d) and 37 CFR § 1.740, and follows the numerical format set forth in 37 CFR § 1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved products are PRELAY™ and REZULIN™. The active ingredient in both PRELAY™ and REZULIN™ is troglitazone.

PRELAY™ is a trademark of Sankyo U.S.A. Corporation, having an office at 780 Third Avenue, Suite 4700, New York, New York 10017. Sankyo U.S.A. Corporation is a subsidiary of Sankyo Co., Ltd.

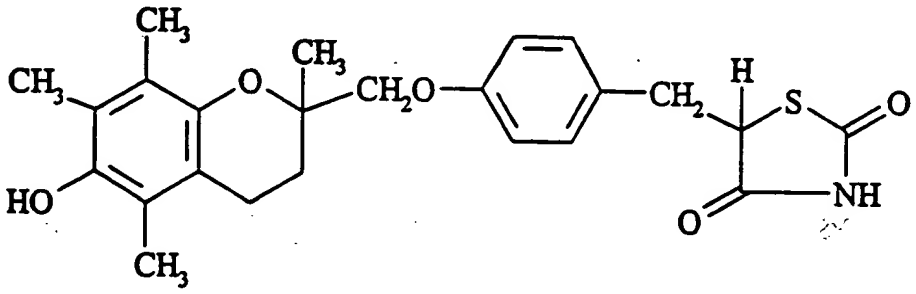
REZULIN™ is a trademark of the Warner-Lambert Company. The Warner-Lambert Company, which has places of business at 201 Tabor Road, Morris Plains, New Jersey 07950 and 2800 Plymouth Road, P.O. Box 1047, Ann Arbor, Michigan 48106-1047, has been licensed in the United States by the Applicant, Sankyo, under United States Patent No. 4,572,912. A LETTER OF THE LICENSEE, of the Warner-Lambert Company, is being submitted concomitantly herewith which provides authorization to Sankyo Co., Ltd. to rely on the activities and data of the Warner-Lambert Company including its Parke-Davis Pharmaceutical Research Division before the Food and Drug Administration in obtaining approval of the drug REZULIN™ for the purpose of obtaining a patent term extension for United States Patent No. 4,572,912.

Troglitazone is designated chemically as (±)-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione. Troglitazone can also be designated chemically as (±)-5-[4-(6-hydroxy-2,5,7,8-

tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione. The empirical formula of troglitazone is $C_{24}H_{27}NO_5S$ and has a molecular weight of 441.55 daltons.

Troglitazone is also known as "CS-045", "CI-991", "GR92132X" and "PD137070".

The plane structural formula of troglitazone is as follows:



PRELAY™ (troglitazone) and REZULIN™ (troglitazone) are both a pharmaceutical for oral administration. The Product Information sheet for the approved product (hereinafter the term "product" or "approved product" refers to both PRELAY™ and REZULIN™) is the PACKAGE INSERT. A copy of the PACKAGE INSERT for PRELAY™ (containing FDA handwritten notations) is attached to Exhibit 2A. It is noted that the trademark REZULIN™ in said PACKAGE INSERT for PRELAY™ should be the trademark --PRELAY™--. A copy of the PACKAGE INSERT for REZULIN™ at the time of approval is enclosed herewith as Exhibit 1. Exhibit 1 corresponds to the PACKAGE INSERT attached to Exhibit 2A.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under § 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 USC § 301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

PRELAY™ (troglitazone) and REZULIN™ (troglitazone) were both approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to § 505(b) of the FFDCA on January 29, 1997; see Exhibit 2A (APPROVAL LETTER for PRELAY™) and Exhibit 2B (APPROVAL LETTER for REZULIN™).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in both PRELAY™ and REZULIN™ is troglitazone. Neither troglitazone, nor any salt or ester of troglitazone, nor any other form of troglitazone have been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on January 29, 1997, and the last day within the sixty (60) day period permitted for submission of an application for extension (pursuant to 37 CFR 1.720(f)) of the patent is March 29, 1997. The date of submission of the present application is no later than March 29, 1997, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No.:		4,572,912
Issue Date	:	February 25, 1986
Inventors	:	Takao YOSHIOKA, Eiici KITAZAWA, Tomoyuki KURUMADA, Mitsuo YAMAZAKI and Kazuo HASEGAWA, all of Japan
Title	:	THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM
Application Serial No.	:	06/644,996
Application Filing Date	:	August 28, 1984
Expiration Date (unless extended)	:	August 28, 2004

The application is assigned from the inventors to the Applicant by an assignment recorded on August 28, 1984, in the United States Patent and Trademark Office at Reel 4313, Frames

986 and 987. A copy of the recorded Assignment is attached as Exhibit 3.

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,572,912 is attached as Exhibit 4 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer or reexamination certificate has been issued.

A Certificate of Correction for United States Patent No. 4,572,912 was issued on January 20, 1987. A copy of said Certificate of Correction is attached herewith as Exhibit 5.

Maintenance fee payments were made to the U.S. Patent and Trademark Office for United States Patent No. 4,572,912 on April 25, 1989 and March 22, 1993. Copies of the receipts for such maintenance fee payments, received from the Patent and Trademark Office, are attached hereto as Exhibit 6.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

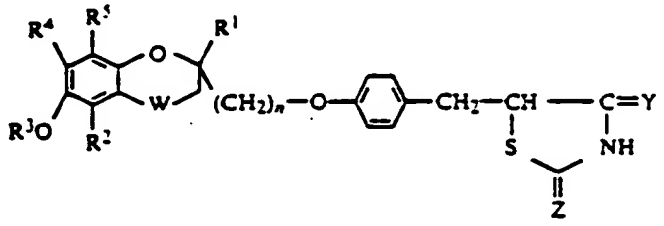
United States Patent No. 4,572,912 claims troglitazone (PRELAY™ and REZULIN™). Both PRELAY™ and REZULIN™ are in tablet form. Both PRELAY™ and REZULIN™ are approved in tablet strengths of 200 mg/tablet and 400 mg/tablet.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 19, 24, 25, 26,

27, 28, 29, 30, 31, 32, 33, 34 and 35, which were allowed in United States Patent No. 4,572,912, each includes troglitazone within its scope. Note in particular the structural formulae set out in Claims 1 and 19 in United States Patent No. 4,572,912.

Claims 1 to 11, 19 and 24 to 35 of United States Patent No. 4,572,912 are set forth as follows:

1. Compounds of formula (I):



in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2-$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

2. Compounds as claimed in claim 1, in which; R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or one of said heterocyclic acyl groups.

3. Compounds as claimed in claim 1, in which: Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1 or C_2 alkoxy group.

4. Compounds as claimed in claim 3, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; n is 1 or 2; and W represents the —CH_2— or >CO group.

5. Compounds as claimed in claim 4, in which R^3 represents a hydrogen atom, a C_1–C_5 aliphatic acyl group, or the benzoyl or nicotinoyl group.

6. Compounds as claimed in claim 5, in which: R^1 and R^4 are the same or different and each represents a C_1–C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

7. Compounds as claimed in claim 1, in which: W represents the —CH_2— or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1–C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

8. Compounds as claimed in claim 7, in which n is 1.

9. Compounds as claimed in claim 7 or claim 8, in which W represents the —CH_2— group.

10. Compounds as claimed in claim 1, selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchro-

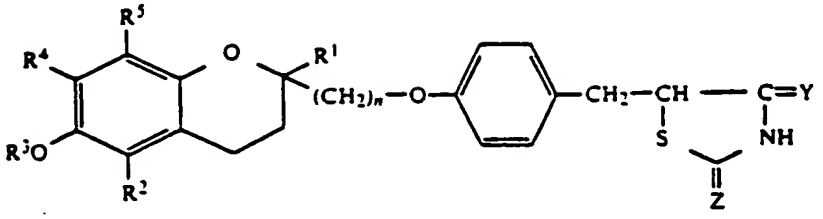
man-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one
5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
5-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

and pharmaceutically acceptable salts thereof.

11. The compound as claimed in claim 1.

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

19. Compounds of formula (Ia):



(Ia)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

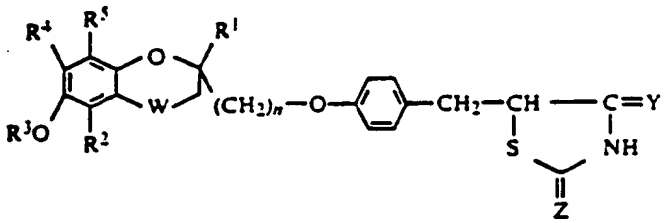
R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substitutents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

24. A pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one active compound in admixture with a pharmaceutically acceptable carrier or diluent, wherein said active compound is selected from compounds of formula (I):



(I)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2-$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

25. Compositions as claimed in claim 24, in which: R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or one of said heterocyclic acyl groups.

26. Compositions as claimed in claim 24, in which: Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1 or C_2 alkoxy group.

27. Compositions as claimed in claim 26, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or $>CO$ group.

28. Compositions as claimed in claim 27, in which R^3 represents a hydrogen atom, a C_1–C_5 aliphatic acyl group, or the benzoyl or nicotinoyl group.

29. Compositions as claimed in claim 28, in which: R^1 and R^4 are the same or different and each represents a C_1–C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

30. Compositions as claimed in claim 24, in which: W represents the $-CH_2-$ or $>CO$ group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1–C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

31. Compositions as claimed in claim 30, in which n is 1.

32. Compositions as claimed in claim 30 or claim 17, in which W represents the $-CH_2-$ group.

33. Compositions as claimed in claim 24, wherein said active compound is selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
5-{4-[2-(6-actoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

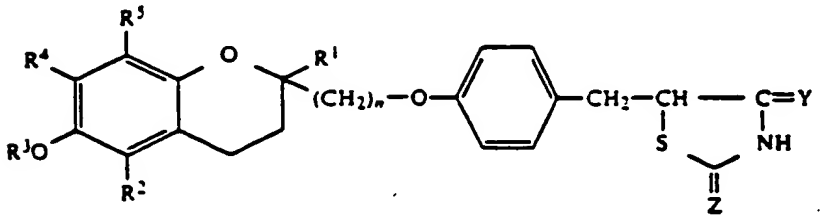
and pharmaceutically acceptable salts thereof.

34. Compositions as claimed in claim 24, wherein said active compound is selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

and pharmaceutically acceptable salts thereof.

35. Compositions as claimed in claim 24, in which said active compound is selected from compounds of formula (1a):



(1a)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

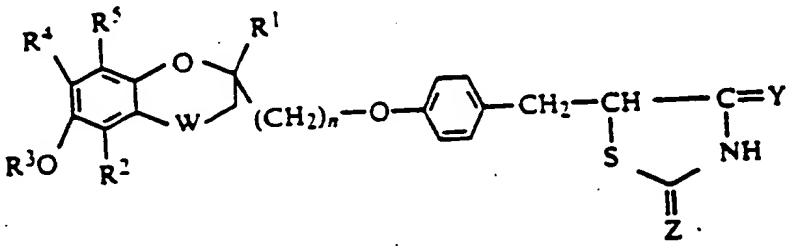
R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

Claim 1

Claim 1 recites compounds of the formula



, wherein R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, R^3 can be

hydrogen, W can be $-CH_2-$, n can be 1 and Y and Z can be oxygen. Thus claim 1 covers troglitazone.

Claim 2

In claim 2, which depends on claim 1, R^3 can be hydrogen. Thus claim 2 covers troglitazone.

Claim 3

In claim 3, which depends on claim 1, Y is oxygen, R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, and R^3 can be hydrogen. Accordingly, claim 3 covers troglitazone.

Claim 4

Claim 4 depends on claim 3 and recites that R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, n can be 1 and W can be $-CH_2-$. Therefore claim 4 covers troglitazone.

Claim 5

Claim 5 depends on claim 4 and recites that R^3 can be a hydrogen atom. Thus claim 5 encompasses troglitazone.

Claim 6

Claim 6 depends on claim 5 and specifies that R^1 and R^4 are each a C_1-C_5 alkyl group. In claim 6, R^2 and R^5 can be a methyl group and R^3 can be hydrogen. Therefore claim 6 covers troglitazone.

Claim 7

Claim 7 depends on claim 1 and specifies that Y and Z are both oxygen atoms. In claim 7, W can be $-CH_2-$, n can be 1, R^1

and R^4 can each be a C_1-C_4 alkyl group, R^2 and R^5 can be a methyl group and R^3 can be hydrogen. Accordingly, troglitazone is covered by claim 7.

Claim 8

Claim 8 depends on claim 7 and calls for n to be 1. Thus claim 8 covers troglitazone.

Claim 9

In claim 9, which depends on claims 7 and 8, W is specified as a $-CH_2-$ group. Accordingly, troglitazone is embraced by claim 9.

Claim 10

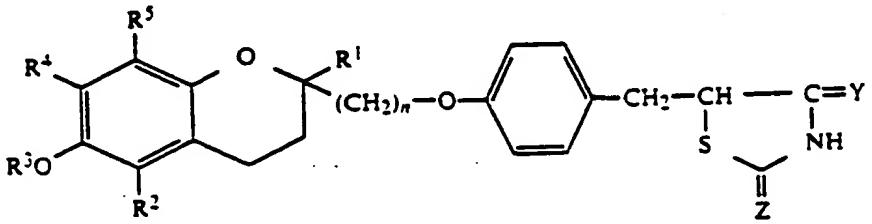
Claim 10 depends on claim 1. The first compound recited in claim 10 is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, which is troglitazone.

Claim 11

Claim 11 of United States Patent No. 4,572,912 specifically recites 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof. Troglitazone is thus covered by claim 11.

Claim 19

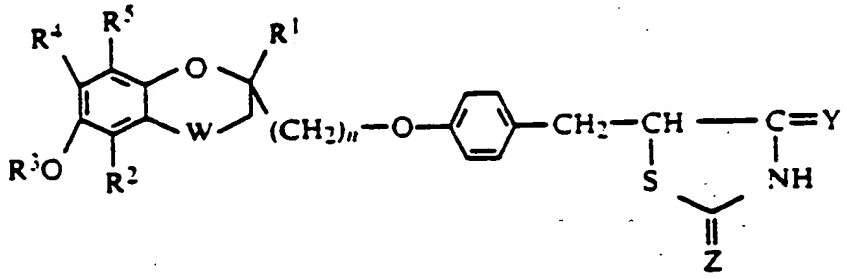
Claim 19 recites compounds of the following formula:



In claim 19, R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, R^3 can be hydrogen, n can be 1, and Y and Z can each be an oxygen atom. Thus claim 19 covers troglitazone.

Claim 24

Claim 24 recites a pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one active compound in admixture with a pharmaceutically acceptable carrier or diluent, wherein the active compound is selected from compounds of formula (I):



wherein R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, R^3 can be hydrogen, W can be $-CH_2-$, n can be 1 and Y and Z can be oxygen. Thus troglitazone is covered by the compounds embraced by claim 24.

Claim 25

Claim 25 depends on claim 24. In claim 24, R^3 can be hydrogen and thus troglitazone is a compound that is covered by claim 25.

Claim 26

Claim 26 depends on claim 24 and specifies that Y is an oxygen atom and R^3 is a hydrogen atom. In claim 26, R^1, R^2, R^4 and R^5 can be a C_1-C_5 alkyl group. Thus troglitazone is one of the compounds defined in claim 26.

Claim 27

Claim 27 depends on claim 26. In claim 26, R^1, R^2, R^4 and R^5 can be a C_1-C_5 alkyl group, n can be 1 and W can be $-CH_2-$. Accordingly, troglitazone is embraced by the compounds defined by claim 27.

Claim 28

Claim 28 depends on claim 27. In claim 28, R^3 can be hydrogen. Therefore troglitazone is covered by the compounds defined by claim 28.

Claim 29

Claim 29 depends on claim 28. In claim 29, R^1 and R^4 can be a C_1-C_5 alkyl group, R^2 and R^5 can be a methyl group and R^3 can be hydrogen. Thus the compounds defined by claim 29 includes troglitazone.

Claim 30

Claim 30 depends on claim 24 and specifies that Y and Z are both oxygen atoms. In claim 30, W can be $-CH_2-$, n can be 1, R^1 and R^4 can be a C_1-C_4 alkyl group, R^2 and R^5 can be a methyl group and R^3 can be hydrogen. Thus troglitazone is covered by the

compounds defined in claim 30.

Claim 31

Claim 31 depends on claim 30 and specifies that n is 1. Accordingly, the compounds defined by claim 31 embrace troglitazone.

Claim 32

Claim 32 depends on claim 30 and specifies that W is the $-CH_2-$ group. Therefore the compounds defined by claim 32 include troglitazone.

Claim 33

Claim 33 depends on claim 24. The first compound recited in claim 33 is 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, which is troglitazone.

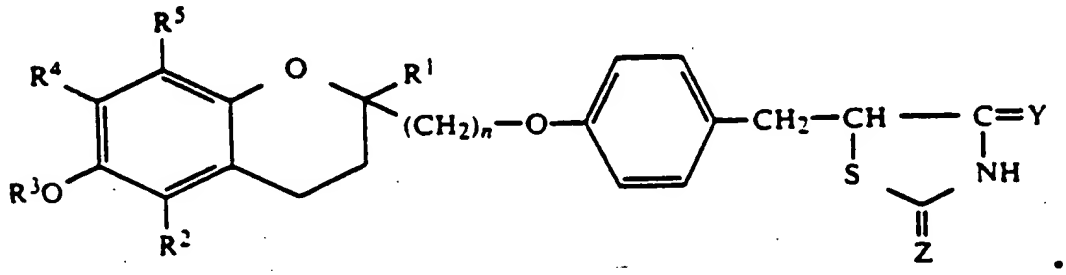
Claim 34

Claim 34 depends on claim 24.

The first compound recited in claim 34 is 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, which is troglitazone.

Claim 35

Claim 35 depends on claim 24 and recites compounds of the following formula:



In claim 35, R^1, R^2, R^4 and R^5 can be C_1-C_5 alkyl, R^3 can be hydrogen, n can be 1 and Y and Z can be oxygen. Thus troglitazone is covered by the compounds defined in claim 35.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 USC § 156(g) in order to enable the Secretary of health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On January 30, 1989, Sankyo submitted to the Food and Drug Administration (hereinafter sometimes referred to as the "FDA") a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for CS-045 (troglitazone). A copy of each of the IND Form FDA 1571 and the IND submission letter (submitted by Oxford Research International Corp. (hereinafter referred to as "Oxford") as the agent for Sankyo) are submitted herewith (along with a copy of a letter dated January 4, 1989 from Sankyo to the FDA appointing Oxford as the agent of Sankyo) as Exhibit 7 (IND SUBMISSION LETTER).

The IND was assigned number 32,703. The IND became effective on March 9, 1989, which is thirty days after receipt of the IND by the FDA; see Exhibit 8 (IND ACKNOWLEDGEMENT LETTER) attached hereto. This establishes the beginning of the

"regulatory review period" under 35 USC § 156(g)(1) as of March 9, 1989.

In a letter dated October 12, 1990 to the Food and Drug Administration by Sankyo U.S.A. Corporation, notification was given that effective October 12, 1990, IND #32,703 was being transferred from Sankyo Co. Ltd., Tokyo, to Sankyo U.S.A. Corporation and that Sankyo U.S.A. Corporation would be the sponsor for IND #32,703. A copy of said October 12, 1990 letter is submitted herewith as Exhibit 9 (OCTOBER 12, 1990 IND TRANSFER LETTER).

In a letter dated April 26, 1991 to the Food and Drug Administration by Sankyo U.S.A. Corporation, the Food and Drug Administration was notified that sponsorship of IND #32,703 was transferred from Sankyo U.S.A. Corporation to the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company. A copy of said April 26, 1991 letter is attached hereto as Exhibit 10A (April 26, 1991 IND TRANSFER LETTER).

In a letter dated May 13, 1991 to the Food and Drug Administration by the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company, the Food and Drug Administration was further notified that sponsorship of IND #32,703 was transferred from Sankyo U.S.A. Corporation to the Parke-Davis Pharmaceutical Research Division of the Warner-

Lambert Company. A copy of said May 13, 1991 letter is attached hereto as Exhibit 10B (MAY 13, 1991 IND TRANSFER LETTER).

On July 31, 1996, a new drug application (NDA 20-719), was submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and § 314.50 of Title 21 Code of Federal Regulations for PRELAY™ (troglitazone) by Sankyo U.S.A. Corporation.

Also on July 31, 1996, a new drug application (NDA 20-720) was submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and § 314.50 of Title 21 Code of Federal Regulations for REZULIN™ (troglitazone) by the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company.

The data contained in both NDA 20-719 and NDA 20-720 were developed by the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company, as well as the Applicant (Sankyo Co., Ltd.), Sankyo U.S.A. Corporation, Sankyo Europe GmbH and Glaxo Wellcome Ltd. (U.K.), a licensee of the Applicant for Europe.

A copy of the cover letter dated July 31, 1996 attached to NDA 20-719 submitted by Sankyo U.S.A. Corporation and the Form FDA 356h are provided herewith as Exhibit 11A (NDA SUBMISSION LETTER).

A copy of the cover letter dated July 31, 1996 attached to the NDA 20-720 of Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company and the Form FDA 356h are provided herewith as Exhibit 11B (NDA SUBMISSION LETTER).

NDA 20-719 for PRELAY™ was approved on January 29, 1997. Attached as Exhibit 2A (APPROVAL LETTER) is a copy of a letter dated January 29, 1997 from the FDA to Sankyo U.S.A. Corporation approving NDA 20-719 for PRELAY™ (troglitazone).

NDA 20-720 for REZULIN™ was approved on January 29, 1997. Attached as Exhibit 2B (APPROVAL LETTER) is a copy of a letter dated January 29, 1997 from the FDA to the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company approving NDA 20-720 for REZULIN™ (troglitazone).

Thus, for the purposes of determining the "regulatory review period" under 35 USC § 156(g)(1), January 29, 1997 is the date of the first approval of troglitazone, which is the active ingredient in both PRELAY™ and REZULIN™.

Summary of the Most Relevant Dates:

January 30, 1989:	IND for troglitazone submitted
March 9, 1989:	IND 32,703 for troglitazone became effective
July 31, 1996:	NDA 20-719 for PRELAY™ and NDA 20-720 for REZULIN™ were submitted
January 29, 1997:	NDA 20-719 for PRELAY™ and NDA 20-720 for REZULIN™ were approved

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10) above, an IND for troglitazone (PRELAY™ and REZULIN™) was submitted on January 30, 1989, which became effective on March 9, 1989. The studies under the IND are summarized in the attached Exhibit 12 (IND LOG)*. These studies were used to support both NDA 20-719 submitted on July 31, 1996 by Sankyo U.S.A. Corporation and NDA 20-720 submitted on July 31, 1996 by the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company.

Subsequent to the submission of the aforesaid NDAs, Warner-Lambert Company personnel had numerous contacts and meetings with FDA personnel with respect to the new drug application and these are summarized in the attached Exhibit 13, (NDA LOG)*.

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* Confidential and non-relevant material has been redacted.

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension

Under § 35 USC 156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 USC § 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and § 156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here as follows:

U.S. Patent No. 4,572,912

(1) The statutory term of U.S. Patent No. 4,572,912 expires on August 28, 2004. This Application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This Application is submitted by Sankyo Co., Ltd., the owner of record. This Application is submitted in accordance with 35 USC § 156(d) in that it is submitted within the sixty-day period beginning on the date, January 29, 1997, that the product received permission for marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 USC 156(d).

(4) As evidenced by the January 29, 1997 letters from the FDA, Exhibit 2A, (APPROVAL LETTER) and Exhibit 2B (APPROVAL LETTER), the product was subject to a regulatory review period under § 505(b)(1) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of PRELAY™ (troglitazone) and REZULIN™ (troglitazone) after regulatory review under § 505(b)(1) is the first permitted commercial marketing of troglitazone. This is confirmed by the absence of any approved new drug application under which troglitazone could be commercially marketed prior to January 29, 1997.

U.S. Patent No. 4,572,912

Statement as to Length of Extension Claimed

In Accordance with 37 CFR Section 1.775

The term of U.S. Patent No. 4,572,912 should be extended for a period of 1534 days to November 9, 2008.

The period of extension is determined in accordance with 35 USC § 156 and follows the format set forth in 37 CFR § 1.775(c) and (d).

> 37 CFR § 1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 USC § 156(g)(1)(B), it is the sum of --
>
> (1) The number of days in the period beginning on the date an exemption under subsection (i) of Section 505 or subsection (d) of Section 507 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under Section 351 of the public Health Service Act;

The number of days between the effective date of the initial IND, March 9, 1989, and the initial submission of each of NDA 20-719 and NDA 20-720, July 31, 1996, is a period of 2,702 days and

> (2) The number of days in the period beginning on the date the application was initially submitted for the approved product under Section 351 of the Public Health Service Act, subsection (b) of Section 505 or Section 507 of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of NDA 20-719 and NDA 20-720, July 31, 1996, to approval of NDA 20-719 and NDA 20-720, January 29, 1997, is a period of 183 days.

37 CFR § 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by --

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on March 9, 1989, which were on or before February 25, 1986, the date the patent was issued, is a period of 0 days,

2,702 days minus 0 days equals 2,702 days, and

the number of days in the period of the NDA initial submission of both NDA 20-719 and NDA 20-720 on July 31, 1996, and approval on January 29, 1997, which were on or before February 25, 1986, the date the patent was issued, is a period of 0 days,

183 days minus 0 days equals 183 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 USC § 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the Applicant did not act with due diligence is 0 days,

therefore,

2,702 days minus 0 days equals 2,702 days.

183 days minus 0 days equals 183 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2,702 days equals 1,351 days.

Thus U.S. Patent No. 4,572,912 should be entitled to an extension of 1534 days (1,351 days plus 183 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1534 days to August 28, 2004, the original term of the patent (no terminal disclaimer was made), extends the term to November 9, 2008.

(3) By adding 14 years to the date of approval of the application under Section 351 of the Public Health Service Act, or subsection (b) of Section 505 or Section 507 of the Federal Food, Drug and Cosmetic Act;

Adding 14 years to January 29, 1997, the date of approval of the Application, results in the date of January 29, 2011.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this Section with each other and selecting the earlier date;

The earlier date is November 9, 2008.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this Section with each other and selecting the earlier date;

(A) Adding 5 years to the original expiration date of the patent or earlier date set by terminal disclaimer; and

(A) Adding 5 years to the original expiration date of the patent (August 28, 2004) gives the date of August 28, 2009.

(B) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

(B) Comparing November 9, 2008 and August 28, 2009, the earlier date is November 9, 2008 and therefore the patent term should be extended to November 9, 2008.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the subject patent.

(ii) If a request was submitted for an exemption under Subsection (i) of Section 505 or Subsection (d) of Section 507 of the Federal Food, Drug, or Cosmetic Act before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984, by --

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this Application for extension.

(14) Prescribed Fee:

A check in payment of the prescribed fee for receiving and acting upon the application for extension in the amount of One Thousand Ninety Dollars ($1,090.00) is enclosed herewith.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Herbert Goodman, Esq.
FRISHAUF, HOLTZ, GOODMAN, LANGER & CHICK, P.C.
767 Third Avenue - 25th Floor
New York, New York 10017-2023
(212) 319-4900

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 CFR 1.740.

A signed declaration by the Applicant is submitted herewith in compliance with 37 CFR 1.740(a)(17).

Respectfully submitted,

HERBERT GOODMAN
REG. NO. 17,081

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EXHIBITS

EXHIBIT 1

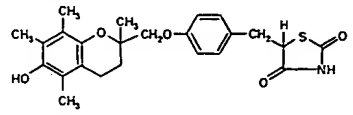
EXHIBIT 1

PACKAGE INSERT FOR REZULIN™

Rezulin™
(Troglitazone) Tablets

DESCRIPTION

Rezulin™ (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Rezulin is used in the management of type II diabetes (noninsulin-dependent diabetes mellitus (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (±-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, or the α-glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 stereoisomers having similar pharmacologic effects. The structural formula is as shown:



Troglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. Troglitazone has a molecular formula of $C_{24}H_{19}NO_5S$ and a molecular weight of 441.55 daltons. It is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrile, anhydrous ethanol, or ether; and practically insoluble in water.

Rezulin is available as 200 and 400 mg tablets for oral administration formulated with the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, povidone, purified water, silicon dioxide, titanium dioxide, and synthetic iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin. It has a unique mechanism of action that is dependent on the presence of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve binding to nuclear receptors (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, troglitazone is not an insulin secretagogue.

In animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type II diabetes. Plasma lactate and ketone body formation are also decreased. The metabolic changes produced by troglitazone result from the increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance. Treatment with troglitazone did not affect pancreatic weight, islet number or glucagon content, but did increase regranulation of the pancreatic beta cells in rodent models of insulin resistance.

Since troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily dose administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (±1 SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	Cmax (µg/mL)	AUC (0-24) (µg·hr/mL)	CL/F* (mL/min)
200	0.90 (0.35)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

*CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (tmax) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 28.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [^{14}C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400 mg dose of [^{14}C]troglitazone after 14 days of treatment with 400 mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Incubation of Metabolite 3 with human liver microsomes suggests that it is not subject to further metabolism.

The inhibitory profile of troglitazone against the 7 major P450 isozymes was characterized using human liver microsomes. Troglitazone was found to inhibit 3A4, 2C9, and 2C19 by 40% to 67% at a concentration of 11 µg/mL. Since the highest peak concentrations expected to be achieved on 600 mg once daily is in the range of 1 to 3 µg/mL, inhibition may not be clinically important. The results of *in vivo* drug interaction studies tend to support this observation (see Drug Interactions); nevertheless, caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

Excretion: Following oral administration of [^{14}C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. Nevertheless, Rezulin should be used with caution in patients with hepatic disease.

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

PARKE-DAVIS

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1C}. These effects are independent of weight loss and persist with Rezulin treatment.

Following Rezulin treatment, LDL, HDL, and total cholesterol (total-C) increase, although total-C/HDL and LDL/HDL ratios do not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Patients treated with Rezulin and concomitant insulin exhibit an initial reduction in triglyceride levels. With the reduction in insulin doses that may occur following Rezulin therapy, some attenuation of the triglyceride reduction may occur.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Rezulin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Rezulin does not stimulate insulin secretion, hypoglycemia in patients treated with Rezulin alone is not to be expected. Because of this insulin-dependent mechanism of action, Rezulin should not be used in patients with type I diabetes.

Clinical Studies

Two clinical studies were conducted to evaluate the effects of Rezulin on glycemic control and insulin dose in patients with type II diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1C} of 9.42 (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were ≤100 mg/dL. Rezulin-treated patients showed a significant ($p<0.0001$) reduction in HbA_{1C} compared with patients who received placebo (see Table 2).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1C} value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p<0.0001$) decrease in exogenous insulin dosage of 15% in the 200 mg Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA_{1C} values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 2. Mean Change From Baseline at 6 Months

Parameter	Placebo	Troglitazone 200 mg	Troglitazone 600 mg
N	118	116	116
HbA_{1c} %			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Mean Change From Baseline (SE)[1]	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference From Placebo (SE)	--	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change From Baseline	-1.3	-8.8	-15.1
Insulin daily dosage, units			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Mean Change From Baseline (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference From Placebo (SE)	--	-12 (3.0)*	-30 (3.0)*
Percent Mean Change From Baseline	1	-15	-42

* $p \leq 0.0001$

[1]Least squares mean adjusted for investigator center and baseline

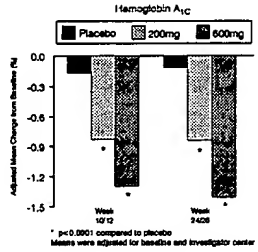


FIGURE 1

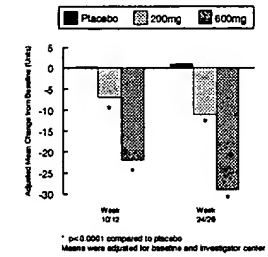


FIGURE 2

A second 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose.

Patients treated with 200 mg (N=75) and 400 mg (N=76) Rezulin had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N=71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400 mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400 mg Rezulin group compared to 7% in the 200 mg group and 1.5% in the placebo group.

A greater than 50% reduction in insulin dose was achieved by 51% of patients on 200 mg and 70% on 400 mg once daily as compared to 17% on placebo.

An extended open-label study of Rezulin (N=17), has followed insulin-treated type II diabetic patients for up to 9 months. Following 9 months of treatment with 400 mg of Rezulin, mean HbA_{1c} levels were decreased by 0.8% compared with baseline values of 11.8% ± 2.0% (mean ± SD). The mean insulin daily dose decreased by 71% (42 units/day) in these seventeen patients.

INDICATIONS AND USAGE

Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1c} >6.5%) despite insulin therapy of over 30 units per day given as multiple injections.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, eg, infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hepatic: During all clinical studies in North America (N=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hypoglycemia: Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. These patients may be at risk for pregnancy.

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4% in troglitazone-treated patients compared with 1 to 2% in those treated with placebo. White blood cell counts also declined slightly in troglitazone-treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (See ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure of parent compound). However, these findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in female rats at 25 and 50 mg/kg at exposures of 5- to 14-fold higher than in humans based on AUC of parent compound. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound that were at least 16-fold higher than the human exposure. No tumors of any type were increased in mice at 50 mg/kg at exposures 2- to 4-fold higher than in humans based on AUC of parent compound.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC at these doses was estimated to be 2- to 8-fold higher than the human exposure.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures based on AUC at these doses were up to 8-fold higher in rats and up to 8-fold higher in rabbits. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures exceeding 14 times the AUC of the 400 mg human dose. Serial echocardiographic evaluations in monkeys treated chronically at maximum achievable exposures (3-5 times the human exposure at the 400 mg dose) did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (eg, congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, caution is advised during the administration of Rezulin to patients with NYHA Class III or IV cardiac status.

ADVERSE REACTIONS

In general, Rezulin is well-tolerated. Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with idiosyncratic drug reaction (See PRECAUTIONS, General).

The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 3. In patients treated with Rezulin in glyburide-controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 3. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 3. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥ 5% of Rezulin-Treated Patients

	% of Patients	
	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed (see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects).

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly (see PRECAUTIONS, General, Hepatic).

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks.The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when tasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Patients With Hepatic Impairment

Rezulin should be used with caution in patients with hepatic disease (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

HOW SUPPLIED

Rezulin is available in 200 and 400 mg tablets as follows:

200 mg Tablets: Yellow, oval, non-scored, film-coated tablet with "PD 352" debossed on one side, and "200" on the other, available in:

N 0071-0352-15 Bottles of 30

N 0071-0352-23 Bottles of 90

N 0071-0352-40 (10 x 10 unit-dose blisters)

400 mg Tablets: Tan, oval, non-scored, film-coated tablet with "PD 353" debossed on one side, and "400" on the other, available in:

N 0071-0353-15 Bottles of 30

N 0071-0353-23 Bottles of 90

N 0071-0353-40 (10 x 10 unit-dose blisters)

Storage

Store at controlled room temperature 20°C-25°C (68°F-77°F). Protect from moisture and humidity.

Caution: Federal law prohibits dispensing without prescription.

January 1997

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
SANKYO PARKE DAVIS
Parsippany, NJ 07054 USA

EXHIBIT 2A

EXHIBIT 2A

APPROVAL LETTER FOR PRELAY™ INCLUDING PACKAGE INSERT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-719

Sankyo U.S.A. Corporation
Attn: David L. Woodward, Ph.D.
Vice President, Development
780 Third Avenue, Suite 4700
New York, NY 10017

JAN 29 1997

Dear Dr. Woodward:

Please refer to your new drug application dated July 31, 1996, received August 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prelay™ (troglitazone) Tablets, 200 mg and 400 mg.

We acknowledge receipt of your submissions dated October 8 and 18, and December 17 and 20, 1996, and January 15 and 24 (2), 1997. The User Fee goal date for this application is August 1, 1997.

This new drug application provides for the use of Prelay Tablets in Type II diabetes patients whose hyperglycemia is inadequately controlled despite insulin therapy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up version of the draft physician labeling submitted by Parke-Davis to NDA 20-720 on January 29, 1997, (with the exception of trade name and company-specific items) and the draft carton and container labels submitted on January 22, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-719. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment as specified in the Parke-Davis submission dated January 10, 1997, to conduct, in conjunction with Parke-Davis, a clinical study in NYHA Class III or IV patients to evaluate whether an increase in plasma volume, which may be observed in patients treated with troglitazone, leads to cardiac decompensation. This study will contain two treatment groups: troglitazone 600 mg/day vs. glyburide. A draft protocol, including the study length and number of patients to be studied, will be submitted to the FDA for approval within three months of the approval of this NDA.

The protocol, data, and final report should be submitted to your IND for this product and a copy of each cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of the commitment. The status summary should include the number of patients entered, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

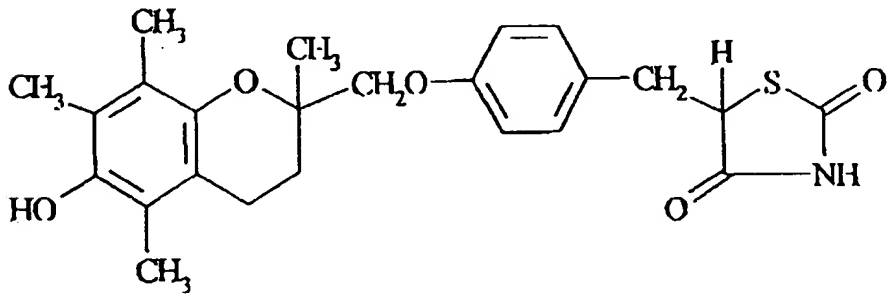
James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Rezulin™
(Troglitazone) Tablets

DESCRIPTION

Rezulin™ (troglitazone) is an oral antihyperglycemic agent which acts primarily by decreasing insulin resistance. Rezulin is used in the management of type II diabetes (noninsulin-dependent diabetes mellitus (NIDDM) also known as adult-onset diabetes). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Troglitazone (±-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) is not chemically or functionally related to either the sulfonylureas, the biguanides, or the α-glucosidase inhibitors. The molecule contains 2 chiral centers, with each of the 4 stereoisomers having similar pharmacologic effects. The structural formula is as shown:



Troglitazone is a white to yellowish crystalline compound; it may have a faint, characteristic odor. Troglitazone has a molecular formula of $C_{24}H_{27}NO_5S$ and a molecular weight of 441.55 daltons. It is soluble in N,N-dimethylformamide or acetone; sparingly soluble in ethyl acetate; slightly soluble in acetonitrile, anhydrous ethanol, or ether; and practically insoluble in water.

Rezulin is available as 200- and 400-mg tablets for oral administration formulated with the following excipients: croscarmellose sodium, hydroxypropyl methylcellulose,

magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, povidone, purified water, silicon dioxide, titanium dioxide, and synthetic iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin. It has a unique mechanism of action that is dependent on the presence of insulin for activity. Troglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Its mechanism of action is thought to involve binding to nuclear receptors (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism. Unlike sulfonylureas, troglitazone is not an insulin secretagogue.

In animal models of diabetes, troglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type II diabetes. Plasma lactate and ketone body formation are also decreased. The metabolic changes produced by troglitazone result from the increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance. Treatment with troglitazone did not affect pancreatic weight, islet number or glucagon content, but did increase regranulation of the pancreatic beta cells in rodent models of insulin resistance.

Since troglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Maximum plasma concentration (Cmax) and the area under plasma concentration-time curve (AUC) of troglitazone increase proportionally with increasing doses over the dose range of 200 to 600 mg/day (Table 1). Following daily drug administration, steady-state plasma concentrations of troglitazone are reached within 3 to 5 days.

TABLE 1. Mean (±1 SD) Steady-State Pharmacokinetics of Troglitazone in 21 Normal Volunteers

Dose (mg/day)	Cmax (μg/mL)	AUC(0-24) (μg·hr/mL)	CL/F* (mL/min)
200	0.90 (0.36)	7.4 (2.4)	500 (187)
400	1.61 (0.69)	13.4 (5.5)	601 (324)
600	2.82 (1.03)	22.1 (6.8)	496 (166)

* CL/F = Apparent oral clearance.

Absorption: Troglitazone is absorbed rapidly following oral administration; the time for maximum plasma concentration (tmax) occurs within 2 to 3 hours. Food increases the extent of absorption by 30% to 85%; thus Rezulin should be taken with a meal to enhance systemic drug availability.

Distribution: Mean apparent volume of distribution (V/F) of troglitazone following multiple-dose administration ranges from 10.5 to 26.5 L/kg of body weight. Troglitazone is extensively bound (>99%) to serum albumin. [^{14}C]troglitazone partitions into red blood cells (~5% of whole blood radioactivity).

Metabolism: In 6 healthy male volunteers given a single 400-mg dose of [^{14}C]troglitazone after 14 days of treatment with 400-mg troglitazone tablets, the major metabolites found in the plasma were the sulfate conjugate (Metabolite 1), followed by the quinone metabolite (Metabolite 3). Only 3.1% of the dose was detected in the urine; this was primarily in the form of the glucuronide conjugate (Metabolite 2), which is present in negligible amounts in the plasma. In both normal volunteers and patients with

type II diabetes, steady-state levels of Metabolite 1 are 6 to 7 times that of troglitazone and Metabolite 3.

Troglitazone incubated with expressed human P450 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, and 3A4 in the presence and absence of known inhibitors of these enzymes showed no Metabolite 3 formation above levels in control samples. Incubation of Metabolite 3 with human liver microsomes suggests that it is not subject to further metabolism.

The inhibitory profile of troglitazone against the 7 major P450 isozymes was characterized using human liver microsomes. Troglitazone was found to inhibit 3A4, 2C9, and 2C19 by 40% to 67% at a concentration of 11 μg/mL. Since the highest peak concentrations expected to be achieved on 600 mg once daily is in the range of 1 to 3 μg/mL, inhibition may not be clinically important. The results of *in vivo* drug interaction studies tend to support this observation (see **Drug Interactions**); nevertheless, caution should be observed when Rezulin is used in combination with drugs known to be metabolized by one of these enzymes. The inhibitory characteristics of Metabolite 3 have not been investigated directly.

Excretion: Following oral administration of [^{14}C]troglitazone, approximately 88% of the radioactivity is recovered in feces (85%) and urine (3%). Unchanged troglitazone is not recovered in urine following oral administration. Mean plasma elimination half-life of troglitazone ranges from 16 to 34 hours.

Special Populations

Renal Insufficiency: In patients with various degrees of renal function, the apparent clearance of total and unbound troglitazone and the plasma elimination half-life of troglitazone, Metabolite 1, and Metabolite 3 do not correlate with creatinine clearance. Thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Troglitazone, Metabolite 1, and Metabolite 3 plasma concentrations in patients with chronic liver disease (Childs-Pugh Grade B or C) were increased by approximately 30%, 400% and 100%, respectively, compared to those in

healthy subjects without hepatic dysfunction. There was no change in plasma protein binding. No adverse events were noted in any group that were attributed to drug. Nevertheless, Rezulin should be used with caution in patients with hepatic disease.

Geriatrics: Steady-state pharmacokinetics of troglitazone, Metabolite 1, and Metabolite 3 in healthy elderly subjects are comparable to those seen in young adults.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of troglitazone and its metabolites are similar in men and women.

Ethnicity: Pharmacokinetics of troglitazone and its metabolites are similar among various ethnic groups.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that Rezulin improves insulin sensitivity in insulin-resistant patients. Rezulin increases insulin-dependent glucose disposal, reduces hepatic gluconeogenesis, and enhances cellular responsiveness to insulin and thus, improves dysfunctional glucose homeostasis. In patients with type II diabetes, the decreased insulin resistance produced by Rezulin causes decreases in serum glucose, plasma insulin, and hemoglobin A_{1c}. These effects are independent of weight loss and persist with Rezulin treatment.

Following Rezulin treatment, LDL, HDL, and total cholesterol increase, total/HDL and LDL/HDL ratios do not change. The increase in total cholesterol is due to the increase in HDL and LDL cholesterol. Despite the observed increase in total and LDL cholesterol, ApoB fraction levels are not increased. Patients treated with Rezulin and concomitant insulin exhibit an initial reduction in triglyceride levels. With the reduction in insulin doses that may occur following Rezulin therapy, some attenuation of the triglyceride reduction may occur.

Pharmacokinetic estimators of systemic troglitazone exposure do not improve the prediction of pharmacodynamic response beyond that obtained based upon knowledge of the administered dose.

Rezulin has only been shown to exert its antihyperglycemic effect in the presence of insulin. Because Rezulin does not stimulate insulin secretion, hypoglycemia in patients treated with Rezulin alone is not to be expected. Because of this insulin-dependent mechanism of action, Rezulin should not be used in patients with type I diabetes.

Clinical Studies

Two clinical studies were conducted to evaluate the effects of Rezulin on glycemic control and insulin dose in patients with type II diabetes who were being treated with insulin.

In one 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetic patients receiving a mean of 73 (range 27-143) units/day of insulin with a mean baseline HbA_{1c} of 9.42 (range 7.04-12.48), Rezulin (200 or 600 mg/day) or placebo was added to the insulin therapy. Investigators were instructed to reduce insulin doses only if two consecutive FSGs were ≤100 mg/dL. Rezulin-treated patients showed a significant ($p < 0.0001$) reduction in HbA_{1c} compared with patients who received placebo (see Table 2).

Thirty percent of patients treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1c} value below 8% at the end of the study compared with 11% of placebo-treated patients. Accompanying this improvement in glycemic control was a significant ($p < 0.0001$) decrease in exogenous insulin dosage of 15% in the 200 mg Rezulin treatment group and 42% in the 600 mg Rezulin treatment group compared with 1% in the placebo group. HbA_{1c} values and insulin dose as a function of duration of Rezulin treatment are presented in Figures 1 and 2.

TABLE 2. Mean Change From Baseline at 6 Months

Parameter	Placebo	Troglitazone 200 mg	Troglitazone 600 mg
N	118	116	116
HbA_{1c} %			
Mean Baseline (SE)	9.43 (0.10)	9.51 (0.10)	9.32 (0.11)
Adjusted Mean Change (SE)[1]	-0.12 (0.10)	-0.84 (0.10)	-1.41 (0.10)
Adjusted Mean Difference from Placebo (SE)	--	-0.72 (0.14)*	-1.29 (0.14)*
Percent Mean Change from Baseline	-1.3	-8.8	-15.1
Insulin daily dosage, units			
Mean Baseline (SE)	75 (3.3)	73 (3.4)	71 (2.9)
Adjusted Mean Change (SE)	1 (2.1)	-11 (2.1)	-29 (2.2)
Adjusted Mean Difference from Placebo (SE)	--	-12 (3.0)*	-30 (3.0)*
Percent Mean Change from Baseline	1	-15	-42

* $p \leq 0.0001$

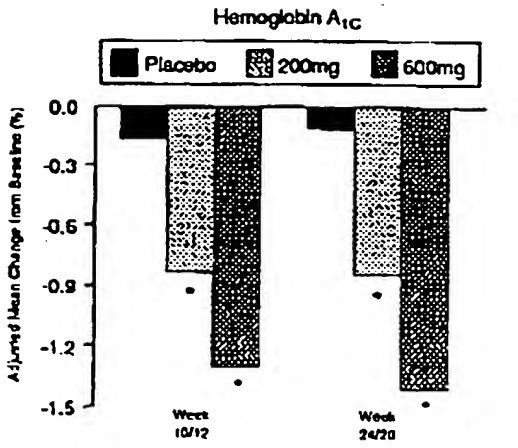
[1] Means were adjusted for baseline and investigator center

FIGURE 1

FIGURE 2

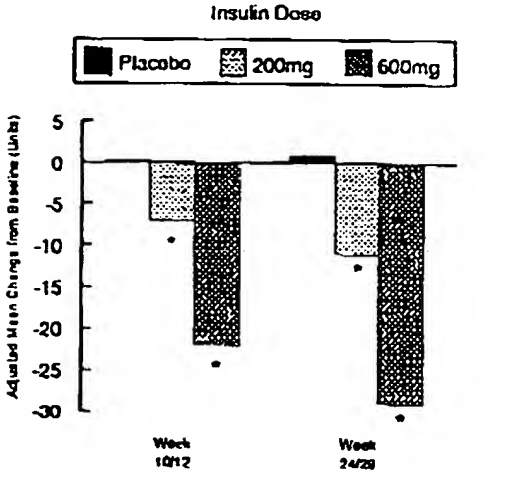
A second 6-month, double-blind, placebo-controlled study in insulin-treated type II diabetics who previously were poorly controlled on oral agents receiving 30 to 150 units insulin/day assessed the use of Rezulin in reducing exogenous insulin dosage while improving glycemic control as measured by capillary blood glucose.

Patients treated with 200-mg (N = 75) and 400-mg (N = 76) Rezulin had their insulin doses decreased by 41% and 58%, respectively, compared to a reduction of insulin dose in the placebo group (N = 71) of 14% while maintaining or improving glycemic control. Forty-one percent of the patients in the 400-mg group decreased their insulin injection frequency an average from 3 to 1 injections per day; 19% of patients receiving placebo decreased their injection frequency an average from 3 to 2 injections per day. Insulin therapy was discontinued in 15% of patients in the 400-mg Rezulin group compared to 7% in the 200-mg group and 1.5% in the placebo group.



*p<0.0001 compared to placebo
Means were adjusted for baseline and investigator center

FIGURE 1



*p<0.0001 compared to placebo
Means were adjusted for baseline and investigator center

FIGURE 2

A greater than 50% reduction in insulin dose was achieved by 51% of patients on 200 mg and 70% on 400 mg once daily as compared to 17% on placebo.

An extended open-label study of Rezulin (n = 17), has followed insulin-treated type II diabetic patients for up to 9 months. Following 9 months of treatment with 400 mg of Rezulin, mean HbA_{1c} levels were decreased by 0.8% compared with baseline values of 11.8% ± 2.0% (mean ±SD). The mean insulin daily dose decreased by 71% (42 units/day) in these seventeen patients.

INDICATIONS AND USAGE

Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1c} >8.5%) despite insulin therapy of over 30 units per day given as multiple injections.

Management of type II diabetes should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only in the primary treatment of type II diabetes, but in maintaining the efficacy of drug therapy. Prior to initiation of Rezulin therapy, secondary causes of poor glycemic control, e.g., infection or poor injection technique, should be investigated and treated.

CONTRAINDICATIONS

Rezulin is contraindicated in patients with known hypersensitivity or allergy to Rezulin or any of its components.

PRECAUTIONS

General

Because of its mechanism of action, Rezulin is active only in the presence of insulin. Therefore, Rezulin should not be used in type I diabetes or for the treatment of diabetic keto-acidosis.

Hepatic: During all clinical studies in North America (n=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hypoglycemia: Patients receiving Rezulin in combination with insulin may be at risk for hypoglycemia and a reduction in the dose of insulin may be necessary. Hypoglycemia has not been observed during the administration of Rezulin as monotherapy and would not be expected based on the mechanism of action.

Ovulation: In premenopausal anovulatory patients with insulin resistance, Rezulin treatment may result in resumption of ovulation. **These patients may be at risk for pregnancy.**

Hematologic: Across all clinical studies, hemoglobin declined by 3 to 4 % in troglitazone-treated patients compared with 1 to 2 % in those treated with placebo. White blood cell counts also declined slightly in troglitazone treated patients compared to those treated with placebo. These changes occurred within the first four to eight weeks of therapy. Levels stabilized and remained unchanged for up to two years of continuing therapy. These changes may be due to the dilutional effects of increased plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Information for Patients

Rezulin should be taken with meals. If the dose is missed at the usual meal, it may be taken at the next meal. If the dose is missed on one day, the dose should not be doubled the following day.

It is important to adhere to dietary instructions and to regularly have blood glucose and glycosylated hemoglobin tested. During periods of stress such as fever, trauma, infection, or surgery, insulin requirements may change and patients should seek the advice of their physician.

When using combination therapy with insulin, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Drug Interactions

Cholestyramine: Concomitant administration of cholestyramine with Rezulin reduces the absorption of troglitazone by approximately 70%; thus, coadministration of cholestyramine and Rezulin is not recommended.

Acetaminophen: Coadministration of acetaminophen and Rezulin does not alter the pharmacokinetics of either drug.

Warfarin: Rezulin has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Sulfonylureas: Coadministration of Rezulin with glyburide does not appear to alter troglitazone or glyburide pharmacokinetics, but may further decrease fasting plasma glucose. There are insufficient data on the use of Rezulin with sulfonylureas to establish the efficacy of this combination.

Metformin: No information is available on the use of Rezulin with metformin.

Ethanol: A single administration of a moderate amount of alcohol did not increase the risk of acute hypoglycemia in Rezulin-treated patients with type II diabetes mellitus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Troglitazone was administered daily for 104 weeks to male rats at 100, 400, or 800 mg/kg and to female rats at 25, 50, or 200 mg/kg. Maximum plasma troglitazone AUC values based on parent compound represent exposures 12- and 47-fold higher for male and female rats, respectively, than human exposure of 400 mg daily. Troglitazone was not carcinogenic in male rats at any dose tested. In female rats, there was a statistically significant increase in sarcomatous tumors at the high dose (47-fold greater than estimated human exposure of parent compound). However, these findings are of unknown clinical relevance as this dose was associated with excessive mortality and is considered to have surpassed the maximum tolerated dose. No tumors of any type were increased in female rats at 25 and 50 mg/kg at exposures of 5- to 14-fold higher than in humans based on AUC of parent compound. In a 104-week study in mice given 50, 400, or 800 mg/kg, incidence of hemangiosarcoma was increased in females at 400 mg/kg and in both sexes at 800 mg/kg; incidence of hepatocellular carcinoma was increased in females at 800 mg/kg. The lowest dose with increased tumor incidence (400 mg/kg) was associated with AUC values of parent compound that were at least 16-fold higher than the human exposure. No tumors of any type were increased in mice at 50 mg/kg at exposures 2- to 4-fold higher than in humans based on AUC of parent compound.

Troglitazone was neither mutagenic in bacteria nor clastogenic in bone marrow of mice. Equivocal increases in chromosome aberrations were observed in an *in vitro* Chinese hamster lung cell assay. In mouse lymphoma cell gene mutations assays, results were equivocal when conducted with a microtiter technique and negative with an agar plate technique. A liver unscheduled DNA synthesis assay in rats was negative.

No adverse effects on fertility or reproduction were observed in male or female rats given 40, 200, or 1000 mg/kg daily prior to and throughout mating and gestation. AUC at these doses was estimated to be 2- to 8-fold higher than the human exposure.

Pregnancy

Pregnancy Category B. Troglitazone was not teratogenic in rats given up to 2000 mg/kg or rabbits given up to 1000 mg/kg during organogenesis. Compared to human exposure of 400 mg daily, estimated exposures based on AUC at these doses were up to 8-fold higher in rats and up to 6-fold higher in rabbits. Body weights of fetuses and offspring of rats given 2000 mg/kg during gestation were decreased. Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats given 40, 200, or 1000 mg/kg during late gestation and lactation periods; no effects were observed in offspring of rats given 10 or 20 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Rezulin should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

It is not known whether troglitazone is secreted in human milk. Troglitazone is secreted in the milk of lactating rats. Because many drugs are excreted in human milk, Rezulin should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Twenty-two percent of patients in clinical trials of Rezulin were 65 and over. No differences in effectiveness and safety were observed between these patients and younger patients.

Use in Patients With Heart Failure

Heart enlargement without microscopic changes has been observed in rodents at exposures exceeding 14 times the AUC of the 400-mg human dose. Serial echocardiographic evaluations in monkeys treated chronically at maximum achievable exposures (3-5 times the human exposure at the 400-mg dose) did not reveal changes in heart size or function. In a 2-year echocardiographic clinical study using 600 to 800 mg/day of Rezulin in patients with type II diabetes, no increase in left ventricular mass or decrease in cardiac output was observed. The methodology employed was able to detect a change of about 10% or more in left ventricular mass.

In animal studies, troglitazone treatment was associated with increases of 6% to 15% in plasma volume. In a study of 24 normal volunteers, an increase in plasma volume of 6% to 8% compared to placebo was observed following 6 weeks of troglitazone treatment.

No increased incidence of adverse events potentially related to volume expansion (e.g., congestive heart failure) have been observed during controlled clinical trials. However, patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during clinical trials. Therefore, caution is advised during the administration of Rezulin to patients with NYHA Class III or IV cardiac status.

Two patients in the clinical studies developed reversible jaundice with findings on liver biopsy consistent with an idiosyncratic drug reaction (see PRECAUTIONS, General).

ADVERSE REACTIONS

In general, Rezulin is well-tolerated. The overall incidence and types of adverse reactions reported in placebo-controlled clinical trials for Rezulin-treated patients and placebo-treated patients are shown in Table 3. In patients treated with Rezulin in glyburide-

controlled studies (N=550) or uncontrolled studies (N=510), the safety profile of Rezulin appeared similar to that displayed in Table 3. The incidence of withdrawals during clinical trials was similar for patients treated with placebo or Rezulin (4%).

TABLE 3. North American Placebo-Controlled Clinical Studies: Adverse Events Reported at a Frequency ≥5% of Rezulin-Treated Patients

	% of Patients	
	Placebo N = 492	Rezulin N = 1450
Infection	22	18
Headache	11	11
Pain	14	10
Accidental Injury	6	8
Asthenia	5	6
Dizziness	5	6
Back Pain	4	6
Nausea	4	6
Rhinitis	7	5
Diarrhea	6	5
Urinary Tract Infection	6	5
Peripheral Edema	5	5
Pharyngitis	4	5

Types of adverse events seen when Rezulin was used concomitantly with insulin (N=543) were similar to those during Rezulin monotherapy (N=1731), although hypoglycemia occurred on insulin combination therapy (see PRECAUTIONS).

Laboratory Abnormalities

Hematologic: Small decreases in hemoglobin, hematocrit, and neutrophil counts (within the normal range) were more common in Rezulin-treated than placebo-treated patients and may be related to increased plasma volume observed with Rezulin treatment. Hemoglobin decreases to below the normal range occurred in 5% of Rezulin-treated and 4% of placebo-treated patients.

Lipids: Small changes in serum lipids have been observed. See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in AST or ALT greater than 3 times the upper limit of normal, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia (>1.25 upper limit of normal) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline, while values for LDH were increased slightly. See PRECAUTIONS, General, Hepatic.

DOSAGE AND ADMINISTRATION

The current insulin dose should be continued upon initiation of Rezulin therapy. Rezulin therapy should be initiated at 200 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of Rezulin should be increased after approximately 2 to 4 weeks. The usual dose of Rezulin is 400 mg once daily. The maximum recommended daily dose is 600 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and Rezulin. Further adjustments should be individualized based on glucose-lowering response. Rezulin should be taken with a meal.

Patients With Renal Insufficiency

Dose adjustment in patients with renal insufficiency is not required (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Patients With Hepatic Impairment

Rezulin should be used with caution in patients with hepatic disease (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

HOW SUPPLIED

Rezulin is available in 200- and 400-mg tablets as follows:

200-mg Tablets: Yellow, oval, non-scored, film-coated tablet with PD 352 debossed on one side, and 200 on the other, available in:

N 0071-0352-15 Bottles of 30
N 0071-0352-23 Bottles of 90
N 0071-0352-40 (10 × 10 unit-dose blisters)

400-mg Tablets: Tan, oval, non-scored, film-coated tablet with PD 353 debossed on one side, and 400 imprinted on the other, available in:

N 0071-0353-15 Bottles of 30
N 0071-0353-23 Bottles of 90
N 0071-0353-40 (10 × 10 unit-dose blisters)

Storage

Store at controlled room temperature, 20°C to 25°C (68°F-77°F). Protect from moisture and humidity.

Caution: Federal law prohibits dispensing without prescription.

January 1997

PARKE-DAVIS
Division of Warner-Lambert Co.
Morris Plains, NJ 07950 USA

Marketed by:
PARKE-DAVIS
Div. of Warner-Lambert Co. and
SANKYO PARKE DAVIS
Parsippany, NJ 07054 USA

EXHIBIT 2B

EXHIBIT 2B

APPROVAL LETTER FOR REZULIN™

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-720

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Irwin G. Martin, Ph.D.
Vice President/FDA Liaison, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, MI 48106-1047

JAN 29 1997

Dear Dr. Martin:

Please refer to your new drug application dated July 31, 1996, received August 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg.

We acknowledge receipt of your submissions dated August 15, 24, 27, and 29, September 5, 12, 16, and 24, October 1, 2, 4, 17, 18, and 28, November 1 (2), 5, 6, 15 (2), and 26, and December 4, 5 (2), 13, and 19, 1996, and January 3, 6, 10, 22, 21, 24, and 29, 1997. The User Fee goal date for this application is August 1, 1997.

This new drug application provides for the use of Rezulin Tablets in Type II diabetes patients whose hyperglycemia is inadequately controlled despite insulin therapy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up version of the draft physician labeling submitted on January 29, 1997, and the draft carton and container labels submitted on January 22, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-720. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment dated January 10, 1997, to conduct a clinical study in NYHA Class III or IV patients to evaluate whether an increase in plasma volume, which may be observed in these patients treated with troglitazone, leads to cardiac decompensation. This study will contain two treatment groups: troglitazone 600 mg/day vs. glyburide. A draft protocol, including the study length and number of patients to be studied, will be submitted to the FDA for approval within three months of the approval of this NDA.

The protocol, data, and final report should be submitted to your IND for this product and a copy of each cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of the commitment. The status summary should include the number of patients entered, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

EXHIBIT 3

EXHIBIT 3

RECORDED ASSIGNMENT

TO: FRISHAUF, HOLTZ, GOODMAN & WOODWARD
261 MADISON AVENUE
NEW YORK, NY 10016

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 YOSHIOKA, TAKAO	DOC DATE: 08/24/84
ASSIGNOR: 002 KITAZAWA, EIICHI	DOC DATE: 08/24/84
ASSIGNOR: 003 KURUMADA, TOMOYUKI	DOC DATE: 08/24/84
ASSIGNOR: 004 YAMAZAKI, MITSUO	DOC DATE: 08/24/84
ASSIGNOR: 005 HASEGAWA, KAZOU	DOC DATE: 08/24/84

RECORDATION DATE: 08/28/84 NUMBER OF PAGES 002 REEL/FRAME 4313/0986

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 SANKYO COMPANY LIMITED 1-6, 3-CHOME NIHONBASHI HONCHO, CHUO-KU TOKYO JAPAN A CORP OF JAPAN

SERIAL NUMBER 6-644996 FILING DATE 08/28/84
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

INVENTOR: 001 YOSHIOKA, TAKAO
INVENTOR: 002 KITAZAWA, EIICHI
INVENTOR: 003 KURUMADA, TOMOYUKI
INVENTOR: 004 YAMAZAKI, MITSUO
INVENTOR: 005 HASEGAWA, KAZOU

ASSIGNMENT

Attorney Docket_____

In consideration of value received, I, having a residence and post office address as stated below next to my name, the sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are listed below) of an invention described in an application for United States patent entitled:

Thiazolidine derivatives, their preparation and compositions containing them

sell and assign to

SANKYO COMPANY LIMITED

a corporation of Japan
having a business address at
1-6,3-chome, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

its successors, assigns or nominees, hereinafter referred to as "Assignee", my entire right, title and interest in and to said invention as disclosed, shown and described in said application for United States patent executed concurrently herewith;

and in and to all applications for patent and patents for said invention, in all countries of the world, including all divisions, reissues, continuations, substitutions and extensions thereof and all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of industrial property, including rights of priority, resulting from the filing of any of said applications; and I authorize and request any official whose duty it is to issue patents, to issue any patent on said invention or resulting therefrom to said Assignee, and I agree that on request and without further consideration, but at the expense of said Assignee, I will communicate to said Assignee or its representatives all facts known to me respecting said invention and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing, reissue, or other applications, make all rightful oaths and declarations, and generally do everything possible to aid said Assignee to obtain and enforce proper patent protection for said invention in all countries.

	INVENTOR: SIGNATURE and DATE		RESIDENCE AND POST OFFICE ADDRESS
201	Sign: Takao Yoshioka Type: Takao Yoshioka	Date: August 24, 1984 Witness:	c/o Chemical Research Laboratories, Sankyo Company Limited, 2-58,1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan
202	Sign: Eiichi Kitazawa Type: Eiichi Kitazawa	Date: August 24, 1984 Witness:	Same as above
203	Sign: Tomoyuki Kurumada Type: Tomoyuki Kurumada	Date: August 24, 1984 Witness:	Same as above
204	Sign: Mitsuo Yamazaki Type: Mitsuo Yamazaki	Date: August 24, 1984 Witness:	c/o Biological Research Laboratories, Sankyo Company Limited, 2-58,1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan

NOTE: TO BE DATED. WITNESS DESIRABLE. LEGALIZATION NOT REQUIRED.

RECORDING OFFICER: After recording, please return to:

FRISHAUF, HOLTZ, GOODMAN & WOODWARD, P.C.
261 Madison Avenue
New York, N. Y. 10016
(212) 972-1400

ASSIGNMENT

Attorney Docket_____

	INVENTOR: SIGNATURE and DATE		RESIDENCE AND POST OFFICE ADDRESS
205	Sign: Kazuo Hasegawa Type: Kazuo Hasegawa	Date: August 24, 1984 Witness:	c/o Biological Research Laboratories, Sankyo Company Limited, 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan
206	Sign: Type:	Date: Witness:	
207	Sign: Type:	Date: Witness:	
208	Sign: Type:	Date: Witness:	
209	Sign: Type:	Date: Witness:	
210	Sign: Type:	Date: Witness:	

EXHIBIT 4

EXHIBIT 4

PATENT

United States Patent [19]

Yoshioka et al.

[11] **Patent Number: 4,572,912**

[45] **Date of Patent: Feb. 25, 1986**

[54] **THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM**

[75] Inventors: **Takao Yoshioka; Eiici Kitazawa; Tomoyuki Kurumada; Mitsuo Yamazaki; Kazou Hasegawa, all of Hiromachi, Japan**

[73] Assignee: **Sankyo Company Limited, Tokyo, Japan**

[21] Appl. No.: **644,996**

[22] Filed: **Aug. 28, 1984**

[30] **Foreign Application Priority Data**

Aug. 30, 1983 [JP] Japan 58-158375

[51] **Int. Cl.**[4] **C07D 417/12; A61K 31/425**

[52] **U.S. Cl.** **514/369; 514/370; 548/183; 548/184; 548/191**

[58] **Field of Search** 548/183, 184, 191; 514/369, 370

[56] **References Cited**

U.S. PATENT DOCUMENTS

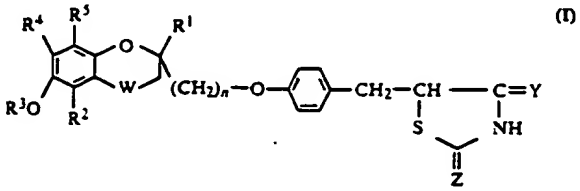
4,340,605	7/1982	Kawamatsu	424/263
4,461,902	7/1984	Kuwomatsu	548/183

Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

[57] **ABSTRACT**

The compounds of formula (I):



(I)

[in which:

R^1 and R^2 are the same or different and each represents hydrogen or C_1–C_5 alkyl;

R^3 represents hydrogen, an acyl group, a (C_1–C_6 alkoxy)carbonyl group or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents hydrogen, C_1–C_5 alkyl or C_1–C_5 alkoxy, or R^4 and R^5 together represent a $C_1$14 C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2-$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents oxygen or imino]

and pharmaceutically acceptable salts thereof have various valuable therapeutic effects on the blood system and may be prepared by a process which includes reacting a corresponding halopropionic acid derivative with thiourea.

39 Claims, No Drawings

THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

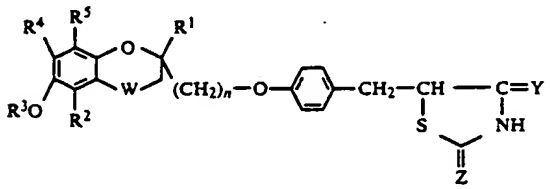
The present invention relates to a series of new thiazolidine derivatives, which we have found to have a variety of valuable biological activities, coupled with an exceedingly low toxicity. The invention also provides processes for preparing the compounds and pharmaceutical compositions containing them.

A number of thiazolidine derivatives are disclosed in European Patent Publication No. 8203 which corresponds to U.S. Pat. No. 4,287,200 and in Chem. Pharm. Bull., 30,3580 (1982). Certain of the thiazolidine derivatives disclosed in these documents have the ability to lower blood lipid and blood sugar levels, although these compounds are a little toxic.

We have now discovered a series of new thiazolidine derivatives which likewise have the ability to lower blood lipid and blood sugar levels and, in addition, have a number of other valuable activities, but which have very low toxicity. In general, the compounds of the invention show blood lipid metabolism ameliorating activity. Specifically, the compounds have the ability to decrease the levels of blood lipid peroxides, blood triglycerides and blood cholesterol.

BRIEF SUMMARY OF THE INVENTION

The compounds of the present invention are compounds of formula (I):



(I)

[in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1–C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1–C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1–C_6 alkoxy)carbonyl group or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

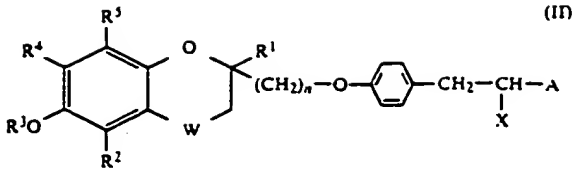
W represents the —CH_2—, >CO or >CH—OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group]

and pharmaceutically acceptable salts thereof.

The invention also provides a process for preparing the compounds of the invention by:

(a) reacting a halopropionic acid derivative of formula (II):



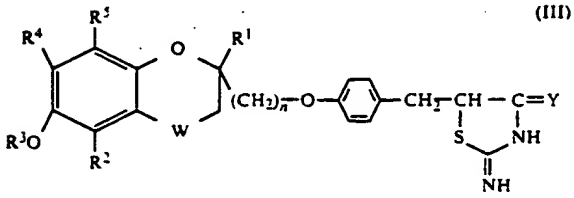
(II)

[in which:

R^1, R^2, R^3, R^4, R^5, n and W are as defined above;

X represents a halogen atom; and

A represents a cyano group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group or a group of formula —$COO(M)_m$, in which M represents a cation and m represents the reciprocal of the valency of the cation M] with thiourea, to give a compound of formula (III):



(III)

(in which R^1, R^2, R^3, R^4, R^5, n, W and Y are as defined above) and then,

(b) if necessary, subjecting said compound to hydrolysis (which may be selective) to prepare said compound of formula (I),

(c) optionally, where W represents a >C=O group, reducing the compound produced in step (a) or step (b) to a compound where W represents a >CH—OH group,

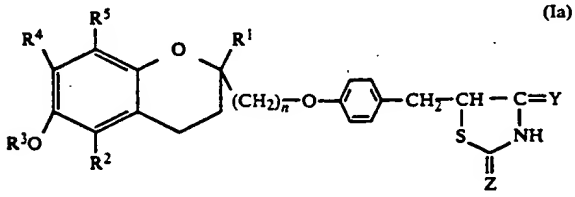
(d) optionally, where W represents a >CH—OH group, acylating the compound to give a compound in which W represents a group of formula >CH—$OR^{6'}$ (in which $R^{6'}$ represents any of the groups defined for R^6 but not the hydrogen atom), and

(e) if necessary, salifying the product.

The invention also provides a pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one compound of the invention in admixture with a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF INVENTION

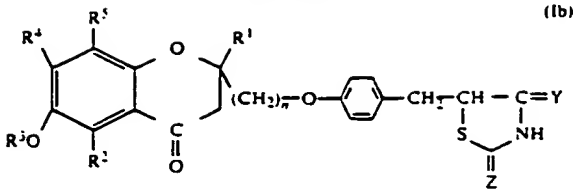
The compounds of the invention, which are 5-[4-(chromanalkoxy)benzyl]thiazolidine derivatives, may be represented by the formulae (Ia), (Ib) and (Ic):



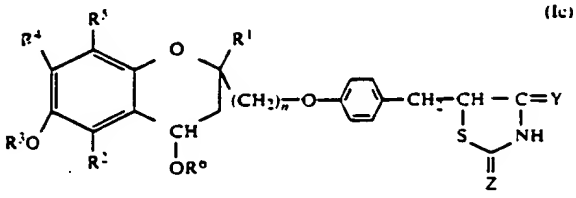
(Ia)

-continued

(Ib)



(Ic)



(in which R^1, R^2, R^3, R^4, R^5, R^6, n, Y and Z are as defined above) and include pharmaceutically acceptable salts thereof.

In the compounds of the invention, where R^1 or R^2 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl group.

Where R^3, R^6 or $R^{6'}$ represents an aliphatic acyl group, this preferably has from 1 to 6 carbon atoms and may include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl and crotonoyl groups. Where R^3, R^6 or $R^{6'}$ represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl or cycloheptanecarbonyl group. Where R^3, R^6 or $R^{6'}$ represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents); examples of such aromatic acyl groups include the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)-benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl and 1-naphthoyl groups. Where R^3, R^6 or $R^{6'}$ represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulfur or nitrogen hetero atoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl (nicotinoyl) and 4-pyridinecarbonyl groups. Where R^3, R^6 or $R^{6'}$ represents an araliphatic acyl group, the aliphatic moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or more substituents (for example nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents); examples of such araliphatic acyl groups include the phenylacetyl, p-chlorophenylacetyl, phenylpropionyl and cinnamoyl groups. Where R^3, R^6 or $R^{6'}$ represents a (C_1–C_6 alkoxy)carbonyl group, the alkyl moiety thereof may be any one of those alkyl groups as defined for R^1 and R^2, but is preferably a methyl or ethyl group, and the alkoxycarbonyl group represented by R^3, R^6 or $R^{6'}$ is therefore preferably a methoxycarbonyl or ethoxycarbonyl group. Where R^3, R^6 or $R^{6'}$ represents an aralkyloxycarbonyl group, the aralkyl moiety thereof may be any one of those included within the araliphatic acyl group represented by R^3, R^6 or $R^{6'}$, but is preferably a benzoyloxycarbonyl group.

Where R^4 and R^5 represent alkyl groups, they may be the same or different and may be straight or branched chain alkyl groups. They preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and isopentyl groups.

Where R^4 and R^5 represent alkoxy groups, these may be the same or different and may be straight or branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. Alternatively, R^4 and R^5 may together represent a C_1–C_4 alkylenedioxy group, more preferably a methylenedioxy or ethylenedioxy group.

Preferred classes of compounds of the present invention are as follows:

(1) Compounds in which R^3 represents a hydrogen atom, a C_1–C_6 aliphatic acyl group, an aromatic acyl group or a heterocyclic acyl group.

(2) Compounds in which Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1–C_5 alkyl group; R^3 represents a hydrogen atom, a C_1–C_6 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1–C_5 alkyl group or a C_1 or C_2 alkoxy group.

(3) Compounds as defined in (2) above, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_1–C_5 alkyl group; n is 1 or 2; and W represents the —CH_2— or >CO group.

(4) Compounds as defined in (3) above, in which R^3 represents a hydrogen atom, a C_1–C_5 aliphatic acyl group, a benzoyl group, or a nicotinoyl group.

(5) Compounds as defined in (4) above, in which: R^1 and R^4 are the same or different and each represents a C_1–C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1–C_4 aliphatic acyl group.

(6) Compounds in which: W represents the —CH_2— or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1–C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1–C_4 aliphatic acyl group.

(7) Compounds as defined in (6) above, in which n is 1.

(8) Compounds as defined in (6) or (7) above, in which W represents the —CH_2— group.

Preferred compounds among the compounds of this invention are those wherein: R^1 is a C_1–C_4 alkyl group, more preferably a methyl or isobutyl group, most preferably a methyl group; R^2 is a hydrogen atom or a C_1–C_4 alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group; R^3 is a hydrogen atom, a C_1–C_4 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl or nicotinoyl group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group;

R^4 is a hydrogen atom, a C_1–C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a methyl, isopropyl, t-butyl or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group; R^5 is a hydrogen atom, a C_1–C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group and most preferably a methyl group; n is 1 or 2, preferably 1; Y is an oxygen atom; Z is an oxygen atom or an imino group, most preferably an oxygen atom; and W is a $—CH_2—$ or $>C=O$ group, preferably a $—CH_2—$ group.

Specific examples of compounds of the present invention are given in the following list:

1. 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
2. 5-[4-(6-hydroxy-2,5,7-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
3. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
4. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione
5. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
6. 5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
7. 5-[4-(6-hydroxy-2,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
8. 5-[4-(6-hydroxy-7-isopropyl-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
9. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
10. 5-[4-(6-hydroxy-2-methyl-7-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
11. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
12. 5-{4-[2-(6-hydroxy-2,5,7-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
13. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
14. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}thiazolidine-2,4-dione
15. 5-{4-[2-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
16. 5-{4-[2-(6-hydroxy-5,7,8-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
17. 5-{4-[2-(6-hydroxy-5,7-diisopropyl-2,8-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
18. 5-{4-[2-(6-hydroxy-7-pentyl-2-propylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
19. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
20. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
21. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
22. 5-[4-(6-hydroxy-2,5-dimethyl-7,8-methylenedioxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
23. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
24. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione
25. 5-{4-[3-(7-t-butyl-6-hydroxychroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione
26. 5-[4-(6-hydroxychroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione
27. 5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
28. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
29. 5-[4-(7-t-butyl-6-hydroxy-2-isopropylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
30. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
31. 5-[4-(6-hydroxy-2-isobutyl-7-isopropylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
32. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-pentylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
33. 5-[4-(6-hydroxy-2-isopentyl-5,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
34. 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
35. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
36. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
37. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
38. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
39. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
40. 5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
41. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
42. 5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
43. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazlidin-4-one
44. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}-2-iminothiazolidin-4-one
45. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
46. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
47. 5-{4-[2-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
48. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
49. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl}-2-iminothiazolidin-4-one
50. 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
51. 5-[4-(6-hydroxy-2,5,7-trimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
52. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
53. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine
54. 5-[4-(7-t-butyl-6-hydroxychroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine
55. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
56. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
57. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
58. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine
59. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine

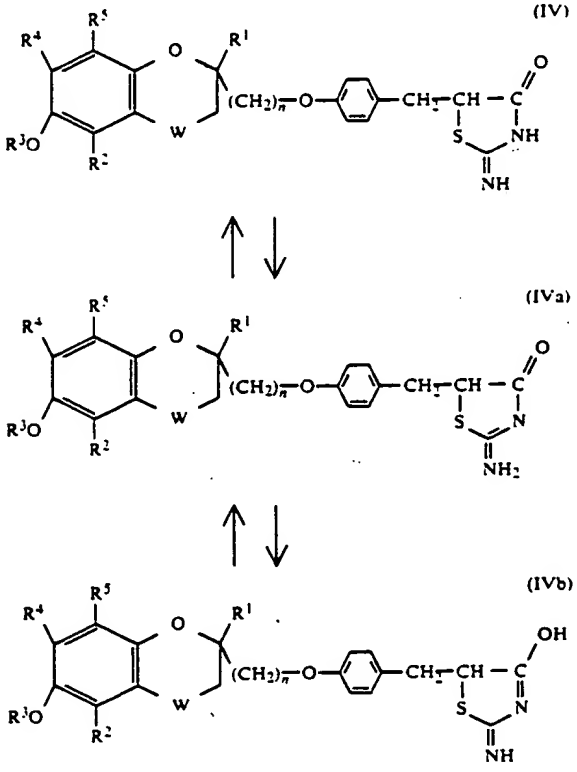
60. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}-2,4-diiminothiazolidine
61. 5-{4-[3-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)propoxy]benzyl}-2,4-diiminothiazolidine
62. 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
63. 5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
64. 5-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
65. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
66. 5-[4-(2-ethyl-6-isobutyryloxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
67. 5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
68. 5-{4-[2-(6-m-fluorobenzoyloxy-2,5,7-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
69. 5-{4-[2-(6-acryloyloxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
70. 5-{4-[2-(6-heptanoyloxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
71. 5-{4-[2-(6-p-aminobenzoyloxy-2-ethyl-5,7,8-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
72. 5-{4-[2-(5,7,8-trimethyl-6-3'-thenoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
73. 5-{4-[2-(6-2'-furoyloxy-5,7-diisopropyl-2,8-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
74. 5-{4-[2-(6-β-naphthoyloxy-7-pentyl-2-propylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
75. 5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
76. 5-{4-[6-(3,5-dichlorobenzoyloxy)-7,8-dimethoxy-5-methylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione
77. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-6-valeryloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
78. 5-[4-(6-isonicotinoyloxy-2,5-dimethyl-7,8-methylenedioxychroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione
79. 5-{4[2-(7,8-dimethoxy-2,5-dimethyl-6-p-nitrobenzoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
80. 5-{4-[3-(6-o-chlorobenzoyloxy-2,5,7,8-tetramethylchroman-2-yl)propyl]benzyl}thiazolidine-2,4-dione
81. 5-{4-[3-(7-t-butyl-6-m-dimethylaminobenzoyloxy-5-methylchroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione
82. 5-[4-(6-acetoxychroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione
83. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione
84. 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
85. 5-[4-(6-acetoxy-5,7-diisopropyl-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
86. 5-{4-[7-t-butyl-6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-2-methylchroman-2-ylmethoxy]benzyl}-2-iminothiazolidin-4-one
87. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
88. 5-[4-(2-ethyl-5,7,8-trimethyl-6-phenylacetoxychroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
89. 5-[4-(6-cinnamoyloxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
90. 5-[4-(6-m-chlorobenzoyloxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
91. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-6-valeryloxychroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
92. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one
93. 5-{4-[2-(6-o-methoxybenzoyloxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
94. 5-{4-[2-(2-methyl-6-pivaloyloxychroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
95. 5-{4-[2-(7-t-butyl-2-methyl-6-propionyloxychroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
96. 5-{4-[2-(6-ethoxycarbonyloxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
97. 5-{4-[2-(6-p-chlorophenylacetoxy-2-ethyl-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
98. 5-{4-[2-(7,8-dimethoxy-5-methyl-6-3'-phenylpropionyloxychroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
99. 5-{4-[3-(6-benzyloxycarbonyloxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl}-2-iminothiazolidin-4-one
100. 5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
101. 5-[4-(6-cyclohexanecarbonyloxy-2,5,7-trimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
102. 5-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
103. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine
104. 5-[4-(6-acetoxy-7-t-butylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine
105. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
106. 5-[4-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
107. 5-[4-(6-acetoxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
108. 5-[4-(6-acetoxy-2-ethyl-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
109. 5-{4-[2-(6-methoxycarbonyloxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine
110. 5-{4-[2-(7-t-butyl-6-cyclopentanecarbonyloxy-2-methylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine
111. 5-{4-[2-(6-formyloxy-2-methylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine
112. 5-{4-[3-(6-methacryloyloxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)propoxy]benzyl}-2,4-diiminothiazolidine
113. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
114. 5-[4-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
115. 5-[4-(6-hydroxy-2,5,7-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

116. 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
117. 5-[4-(7-t-butyl-4,6-dihydroxy-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
118. 5-[4-(6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
119. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
120. 5-[4-(2-ethyl-4,6-dihydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
121. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
122. 5-[4-(6-hydroxy-2,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
123. 5-[4-(6-hydroxy-7-isopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
124. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
125. 5-[4-(6-hydroxy-2-methyl-4-oxo-7-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
126. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
127. 5-{4-[2-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
128. 5-{4-[2-(6-hydroxy-2,5,7-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
129. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
130. 5-{4-[2-(7-t-butyl-4,6-dihydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
131. 5-{4-[2-(6-hydroxy-2-methyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
132. 5-{4-[2-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
133. 5-{4-[2-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
134. 5-{4-[2-(6-hydroxy-5,7-diisopropyl-2,8-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
135. 5-{4-[2-(6-hydroxy-4-oxo-7-pentyl-2-propylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
136. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
137. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
138. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
139. 5-[4-(6-hydroxy-2,5-dimethyl-7,8-methylenedioxy-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
140. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
141. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione
142. 5-{4-[3-(7-t-butyl-6-hydroxy-4-oxochroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione
143. 5-[4-(6-hydroxy-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
144. 5-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
145. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxo-2-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
146. 5-[4-(7-t-butyl-6-hydroxy-2-isopropyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
147. 5-[4-(2-butyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
148. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
149. 5-[4-(4,6-dihydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
150. 5-[4-(2-t-butyl)-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
151. 5-[4-(6-hydroxy-2-isobutyl-7-isopropyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
152. 5-[4-(6-hydroxy-5,7-dimethyl-4-oxo-2-pentylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
153. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-pentyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
154. 5-[4-(6-hydroxy-2-isopentyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
155. 5-{4-[6-hydroxy-5,7,8-trimethyl-2-(2-methylbutyl)-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione
156. 5-{4-[2-(2,2-dimethylpropyl)-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione
157. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
158. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
159. 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
160. 5-[4-(6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
161. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
162. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
163. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
164. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
165. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
166. 5-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
167. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
168. 5-{4-[2-(6-hydroxy-2-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
169. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
170. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
171. 5-{4-[2-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
172. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
173. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)propoxy]benzyl}-2-iminothiazolidin-4-one
174. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
175. 5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

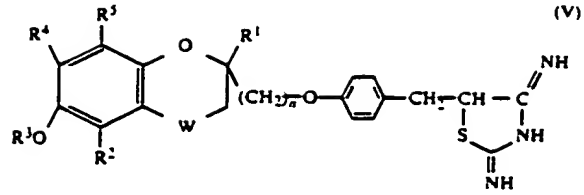
176. 5-[4-(6-acetoxy-4-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
177. 5-[4-(4,6-diacetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
178. 5-[4-(6-acetoxy-4-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
179. 5-[4-(4-acetoxy-6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
180. 5-[4-(4,6-dibenzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
181. 5-[4-(2-ethyl-4,6-diisobutyryloxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
182. 5-[4-(4,6-dibutyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
183. 5-{4-[2-(6-m-fluorobenzoyloxy-4-heptanoyloxy-2,5,7-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
184. 5-{4-[2-(4,6-diacryloyloxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
185. 5-{4-[2-(4-m-fluorobenzoyloxy-6-heptanoyloxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
186. 5-{4-[2-(5,7,8-trimethyl-4,6-bis{3-thenoxyloxy}chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
187. 5-{4-[2-(4,6-bis{2-furoyloxy}-5,7-diisopropyl-2,8-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
188. 5-[4-(2,5,7,8-tetramethyl-4,6-dinicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
189. 5-{4-[4,6-bis(3,5-dichlorobenzoyloxy)-7,8-dimethoxy-5-methylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione
190. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-4,6-divaleryloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
191. 5-{4-[7-t-butyl-6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-2-methyl-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione
192. 5-[4-(2-ethyl-5,7,8-trimethyl-4-oxo-6-phenylacetoxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
193. 5-[4-(6-cinnamoyloxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
194. 5-[4-(6-m-chlorobenzoyloxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
195. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-4-oxo-6-valeryloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
196. 5-{4-[2-(6-o-methoxybenzoyloxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
197. 5-{4-[2-(2-methyl-4-oxo-6-pivaloyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
198. 5-{4-[2-(7-t-butyl-2-methyl-4-oxo-6-propionyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
199. 5-{4-[2-(6-ethoxycarbonyloxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
200. 5-{4-[2-(6-p-chlorophenylacetoxy-2-ethyl-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
201. 5-[4-{2-[7,8-dimethoxy-5-methyl-4-oxo-6-(3-phenylpropionyloxy)chroman-2-yl]ethoxy}benzyl]-thiazolidine-2,4-dione
202. 5-[4-(6-cyclohexanecarbonyloxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine
203. 5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
204. 5-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
205. 5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
206. 5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
207. 5-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
208. 5-{4-[2-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

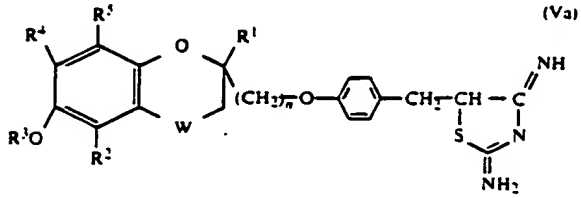
Of the compounds listed above, preferred compounds are Compounds No. 1, 5, 6, 11, 13, 23, 27, 30, 34, 36, 38, 40, 42, 62, 63, 67, 75, 113, 116, 148, 157, 159, 162, 175, 205, 206, and 207. More preferred compounds are Compounds No. 1, 5, 13, 30, 62, 67, 113 and 116 and the most preferred compounds are Compounds No. 1 and 62.

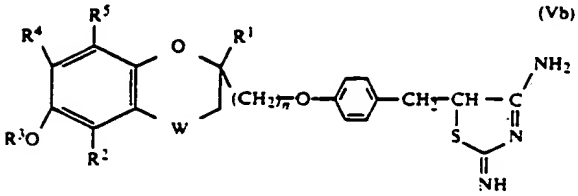
Various of the compounds of the invention can exist in the form of tautomers. For example, those compounds of the invention in which Z represents an imino group and Y represents an oxygen atom can exist in the form of the tautomers (IV), (IVa) and (IVb):



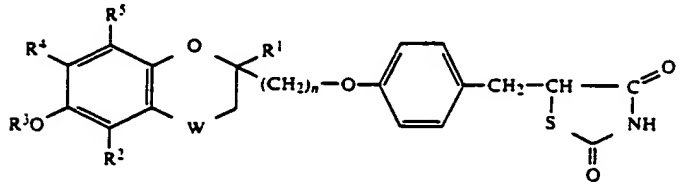
Compounds in which both Y and Z represent imino groups can exist in the form of the tautomers (V), (Va) and (Vb):

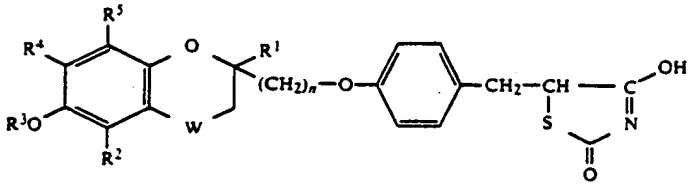

(V)

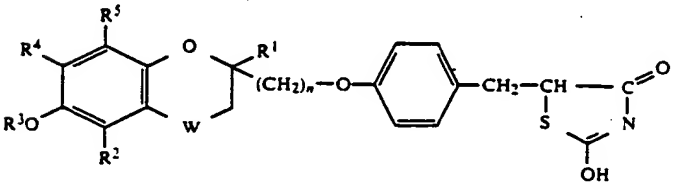

(Va)


(Vb)

compounds in which Y and Z both represent oxygen atoms can exist in the form of the tautomers (VI), (VIa) and (VIb):


(VI)


(VIa)


(VIb)

For convenience, all of the tautomers are represented by a single formula, but the tautomeric nature of these compounds should be remembered, as it can have an effect upon various of the properties of the compounds, including their salt-forming ability, as discussed hereafter.

In addition, the compounds of the invention can exist in the form of various stereoisomers. For example, where W represents a >C=O or —CH_2— group, the carbon atoms at the 2-position of the chroman ring and the 5-position of the thiazolidine ring are both asymmetric. Furthermore, where W represents a >CH—OR^6 group, the carbon atoms at the 2- and 4-positions of the chroman ring and at the 5-position of the thiazolidine ring are asymmetric. All of these thus give rise to the possibility of stereoisomers. All of the isomers are represented herein by a single formula, and the present invention envisages both mixtures of the isomers and the individual isomers, which may be separated from each other by conventional means.

The compounds of the present invention also include salts of compounds of the invention described above, which may be salts with cations. Cations with which the compounds of the invention may form salts include: alkali metals, such as sodium or potassium; alkaline earth metals, such as calcium; and trivalent metals, such as aluminum.

It will, however, be appreciated that the particular nature of the salt employed is not critical to the present invention and any cations known in the art for forming salts of this type may equally be used in the present invention. The only constraint is that the cations should not, or should not to an unacceptable extent, increase the toxicity or reduce the activity of the resulting compound.

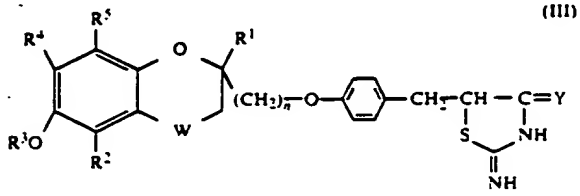
Because the compounds of the invention contain a number of salt-forming centres, mono- and di-salts may be formed. For example, because of the tautomerism described above in relation to the compounds of for-

mula (VI), there are two potential salt-forming reactive sites at the oxygen atom in the group $—OR^3$ and the nitrogen atom at the 3-position of the thiazolidine ring.

PREPARATION OF NEW COMPOUNDS

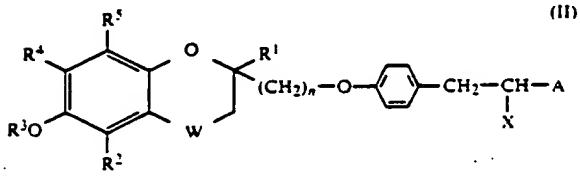
Step (a)

Compounds of the invention in which Z represents an imino group, that is to say compounds of formula (III):



(III)

(in which R^1–R^5, n, W and Y are as defined above) may be prepared by reacting a compound of formula (II):



(II)

[in which R^1–R^5 and n are as defined above, A represents a cyano group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group or a group of formula $—COO(M)_m$, in which M represents a cation and m is the reciprocal of its valency, and X represents a halogen atom] with thiourea.

Where A represents a cyano group, the product is a compound in which Y represents an imino group; where A represents a carboxy, alkoxycarbonyl, carbamoyl or $—COO(M)_m$ group, the product is a compound where Y represents an oxygen atom.

In the above formula (II), where A represents an alkoxycarbonyl group, this is preferably a (C_1–C_6 alkoxy)carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or butoxycarbonyl group. M preferably represents a metal atom, such as a sodium, potassium, calcium or aluminum atom, or an ammonium group. X preferably represents a chlorine, bromine or iodine atom.

This reaction is preferably applied only to those compounds where W represents a $—CH_2—$ or $>C=O$ group, compounds in which W represents a $>CH—OR^6$ group being prepared from the corresponding compound where W represents a $>C=O$ group, as explained hereafter.

Reaction of the compound of formula (II) with thiourea is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction. Suitable solvents include: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; ethers, such as tetrahydrofuran or dioxane; ketones, such as acetone; dimethyl sulfoxide; sulfolane; or amides, such as dimethylformamide.

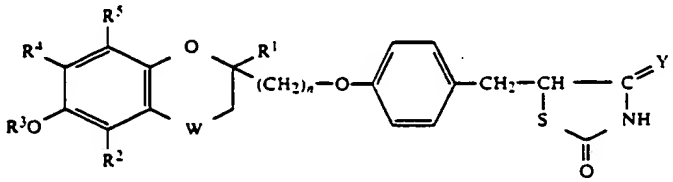
There is no particular limitation on the molar ratio of the compound of formula (II) to thiourea; however, we would normally prefer to use equimolar amounts of a molar excess of thiourea, preferably a slight molar excess. In general, from 1 to 2 moles of thiourea per mole of the compound of formula (II) are preferred.

The various reaction conditions, such as the reaction temperature and time, will vary, depending upon the natures of the starting materials and the solvent; however, the reaction is normally effected at the reflux temperature of the solvent or at a temperature of from 80° to 150° C. for a period of from 1 to 20 hours.

The resulting compound of formula (III) may be the desired final product of the present invention, in which case it may be isolated from the reaction mixture by conventional means, as discussed hereafter. Alternatively, with or without isolation and/or purification, the compound of formula (III) may be subjected to one or both of steps (b) and (c), in any order, and, if desired, step (c) may be followed by step (d). The product of any of these steps may be subjected to the salification reaction discussed in step (e).

Step (b)

In this step, the compound of formula (III), that is to say a compound of formula (I) in which Z represents an imino group, may be hydrolysed to give the corresponding compound of formula (I) in which Z represents an oxygen atom, that is to say a compound of formula (VII):



(VII)

(in which R^1–R^5, n, W and Y are as defined above).

The hydrolysis reaction is preferably carried out by heating the compound of formula (III) in a suitable solvent with water and an organic acid (such as acetic acid) or a mineral acid (such as sulfuric acid or hydrochloric acid). The nature of the solvent is not critical to the invention, provided that it has no adverse effect upon the reaction; suitable solvents include: sulfolane; and alcohols, such as methanol, ethanol or ethylene glycol monomethyl ether.

The amount of acid used is preferably from 0.1 to 10 moles, more preferably from 0.2 to 3 moles, per mole of the compound of formula (III). The water or aqueous solvent is preferably employed in a large molar excess over the compound of formula (III).

Although not critical, the temperature employed for the reaction is preferably from 50° to 100° C. and the time required for the reaction is normally from 2 to 20 hours.

Where Y in the compound of formula (III) represents an imino group, the hydrolysis of the present step will normally likewise convert said imino group to an oxy-

gen atom, the product being a compound in which both Y and Z are oxygen atoms. However, by careful control of the hydrolysis conditions, it is possible to prevent the hydrolysis reaction going to completion, in which case part of the product will be a compound in which Y represents an imino group and Z represents an oxygen atom.

In addition to converting the imino group represented by Z to an oxygen atom, where R^3 in the compound of formula (III) represents an acyl group, the hydrolysis reaction may convert this to a hydrogen atom, although it is possible to maintain the acyl group represented by R^3 intact, provided that appropriate reaction conditions are chosen, as is well-known in the art.

Where the compound of formula (VII) is a compound in which R^3 represents a hydrogen atom, this may be acylated to give a corresponding compound in which R^3 represents one of the acyl groups defined above.

This acylation reaction may be carried out at any suitable stage in the reaction sequence and may, if desired, be carried out simultaneously with the acylation reaction of step (d), as described hereafter. Where, however, the acylation reaction is carried out separately from step (d), the conditions are preferably as follows:

The acylating agent is preferably an acid halide or an acid anhydride, or it may be an organic acid, such as an aromatic carboxylic acid or an aliphatic carboxylic acid, in association with a dehydrating agent or dehydrating catalyst such as a mineral acid (e.g. hydrochloric acid or sulfuric acid) or an organic acid (e.g. p-toluenesulfonic acid).

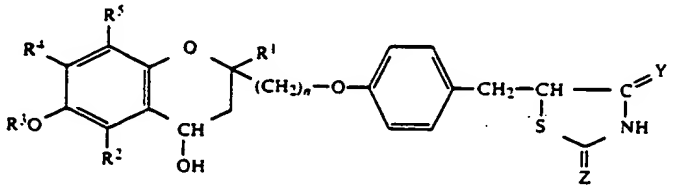
The reaction is normally carried out in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene or toluene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, such as methylene chloride or chloroform; ketones, such as acetone or methyl ethyl ketone; amides, such as dimethylformamide or dimethylacetamide; organic bases, such as pyridine or triethylamine; sulfoxides, such as dimethyl sulfoxide; sulfones, such as sulfolane; or water; a single one of these solvents or a mixture of any two or more thereof may be employed.

The ratio of the amount of the compound of formula (VII) in which R^3 represents a hydrogen atom to the amount of acylating agent is not particularly critical, but the use of a slight molar excess of the acylating agent over the compound of formula (VII) may be desirable. In general, we prefer to employ from 1 to 2 moles of acylating agent per mole of compound of formula (VII).

The reaction conditions, such as the reaction temperature and reaction time, will vary, depending upon a number of factors, including the nature of the starting materials and solvent, but the reaction is generally carried out at a temperature of from 0° to 100° C. for a period of from several minutes to about 20 hours.

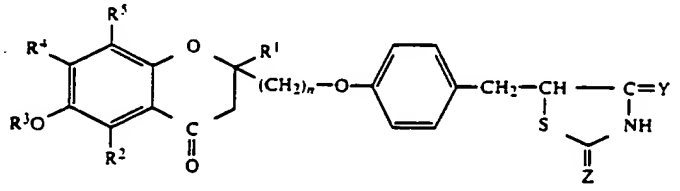
Step (c)

Compounds of formula (I) in which W represents a group of formula >CH—OH, that is to say compounds of formula (Id):



(Id)

(in which R^1-R^5, n, Y and Z are as defined above) may be prepared by reducing the corresponding compound in which W represents a group of formula >C=O, that is to say a compound of formula (Ib):



(Ib)

(in which R^1-R^5, n, Y and Z are as defined above).

The reducing agent employed for this reaction is any one which is capable of reducing a ring carbonyl group to a >CH—OH group without affecting, or affecting to a substantial degree, the remainder of the molecule. Suitable reducing agents include borohydrides, such as sodium borohydride, or K-Selectride, especially sodium borohydride.

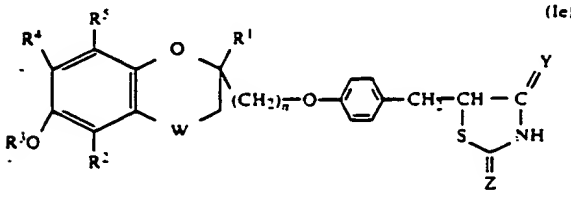
The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; and ethers, such as tetrahydrofuran or dioxane.

The molar ratio of the compound of formula (Ib) to the reducing agent is not critical, however we prefer to employ a molar excess of reducing agent, preferably from 1 to 20 moles of reducing agent (especially sodium borohydride) per mole of compound of formula (Ib).

The reaction conditions, particularly the reaction temperature and time, will vary depending upon a number of factors, especially the natures of the starting material, solvent and reducing agent. However, the reaction is normally carried out at a temperature of from 0° to 100° C. for a period of from 1 to about 20 hours.

Step (d)

Optionally, compounds of formula (I) in which W represents a group of formula >CH—OR$^{6'}$ (in which R$^{6'}$ represents any one of the groups defined for R^6 but not the hydrogen atom), that is to say compounds of formula (Ie):



(Ie)

(in which R^1–R^5, R$^{6'}$, n, Y and Z are as defined above) may be prepared by acylating the corresponding compound of formula (Id), prepared as described in step (c).

The acylating agent is preferably an acid halide or acid anhydride, the parent acid of which will depend upon the acyl group R$^{6'}$ which is desired to be introduced into the compound.

The acylation reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, such as methylene chloride or chloroform; organic bases, such as pyridine or triethylamine; amides, such as dimethylformamide or dimethylacetamide; sulfoxides, such as dimethyl sulfoxide; and sulfones, such as sulfolane.

The ratio of the amount of compound of formula (Id) to the acylating agent is not particularly critical and we therefore prefer to employ a slight molar excess of acylating agent over compound (Id). In general, from 1 to 2 moles of acylating agent are employed per mole of compound of formula (Id).

The reaction conditions, particularly reaction temperature and time, will vary depending upon a number of factors, especially the natures of the starting material, acylating agent and solvent, but we normally prefer to carry out the reaction at a temperature of from 0° to 100° C. for a period of from several minutes to about 20 hours.

Step (e)

The compounds of the invention, prepared as described in any of the above steps may be converted to their salts by conventional means, for example by reaction with a basic compound of an alkali metal (such as sodium or potassium), an alkaline earth metal (such as calcium) or a trivalent metal (such as aluminum). Preferred such compounds are sodium hydroxide, potassium hydroxide, sodium ethoxide and potassium t-butoxide.

It will be appreciated that the compounds produced in all of the above steps can exist in various tautomeric forms, as illustrated in relation to compounds (IV), (V) and (VI).

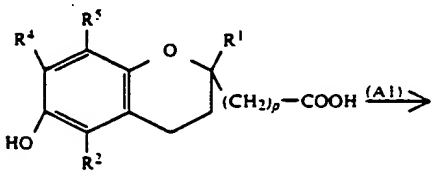
The compounds prepared as described in any of the above steps may be separated after that step and, if desired, purified by conventional means. Suitable isolation and purification steps include concentration of the reaction mixture by evaporating off the solvent under reduced pressure, extraction with a suitable solvent, recrystallization, transfer into another solvent, chromatography and optical resolution. However, where two or more of the above steps are to be carried out, they may, if desired, be carried out without intermediate isolation or purification.

PREPARATION OF STARTING MATERIALS

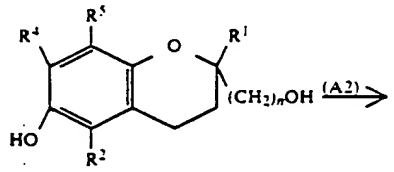
The α-halocarboxylic acid derivatives of formula (II), which are the principal starting materials for preparing the compounds of the invention, are novel compounds and may be prepared by Methods A and B described below.

Method A

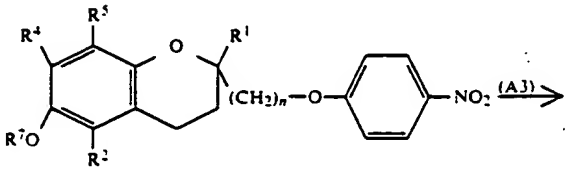
Compounds of formula (II) in which W represents a —CH$_2$— group may be prepared by the sequence of reactions illustrated in the following reaction scheme:



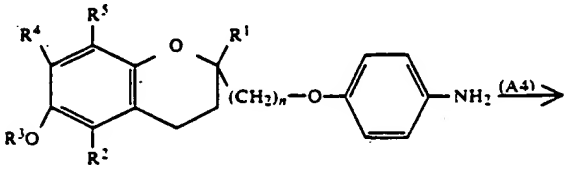
(VIII)



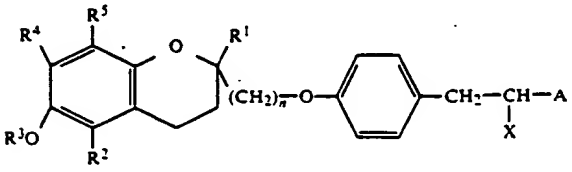
(IX)



(X)



(XI)



(IIa)

In the above formulae, R^1–R^5, n, A and X are as defined above, p=(n−1); and R^7 represents a hydroxy-protecting group.

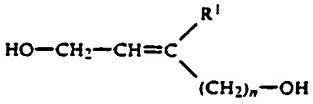
Step (A1)

The chroman carboxylic acid homologs (VIII), which are the starting materials for this Method, may be prepared as described, for example, in the Journal of the American Oil Chemical Society, 51, 200 (1974).

These acids (VIII) are reduced with a reducing agent, such as lithium aluminum hydride or Vitride [sodium bis(2-methoxyethoxy)aluminum hydride], to give the corresponding chroman alcohol homolog (IX). This reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene or xylene; and aliphatic hydrocarbons, such as hexane, heptane, cyclohexane, petroleum ether, ligroin or ethylcyclohexane.

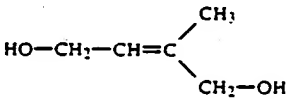
The ratio of the amount of acid (VIII) to reducing agent is not particularly critical, but we generally prefer to use a slight molar excess of reducing agent. Preferably the amount of reducing agent is from 1 to 2 moles per mole of acid (VIII). The reaction conditions, particularly the reaction temperature and time, will vary depending upon a number of factors, such as the nature of the starting material, the reducing agent and the solvent, but the reaction is generally carried out at a temperature of from 10° to 100° C. for a period of from 10 minutes to 20 hours.

Alternatively, the chroman alcohol homolog (IX) may be prepared by reacting a hydroquinone with a compound of formula (XII):



(XII)

(in which n and R^1 are as defined above), e.g. a compound of formula (XIIa):



(XIIa)

in the presence of aluminum chloride, as described in West German Pat. No. 3,010,504.

Step (A2)

The chroman alcohol homologs of formula (IX) obtained in step (A1) may be converted to the corresponding nitrophenoxyalkyl chroman compounds (X). However, before carrying out this reaction, we prefer that the phenolic hydroxy group should be protected by a hydroxy-protecting group R^7.

The nature of the hydroxy-protecting group is not critical and any such group commonly used in this type of reaction and compound may be employed. Suitable groups include: alkoxyalkyl groups, such as the methoxymethyl group; aralkyl groups, such as the benzyl group; the 2-tetrahydropyranyl group; and acyl groups, such as the acetyl or benzoyl groups. The alkoxyalkyl groups are preferred. The reaction is normally effected by contacting a compound R^7X (in which R^7 is as defined above and X represents a halogen atom, preferably a chlorine atom), such as chloromethyl methyl ether or benzyl chloride, with the compound of formula (IX) in the presence of a base such as an alkali metal or alkaline earth metal hydride (e.g. sodium hydride or calcium hydride) or an alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide). The reaction is normally carried out in the presence of a solvent, for example: an ether, such as diethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an aliphatic hydrocarbon, such as hexane or heptane; an amide, such as dimethylformamide or dimethylacetamide; a sulfoxide, such as dimethyl sulfoxide; or a sulfone, such as sulfolane. There is no particular limitation on the molar ratio of compound (IX) to the compound R^7X, but we generally prefer to use a slight molar excess of the compound (IX), in order to reduce the risk of protecting the hydroxy group in the side chain at the 2-position. In general, we prefer to employ from 0.8 to 1 mole of the compound R^7X per mole of the compound (IX). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the nature of the starting material, the compound R^7X and the solvent, but we normally prefer a reaction temperature of from 0° to 50° C. and a time of from several minutes to several tens of minutes.

The protected chroman alcohol produced by this reaction can, if desired, be isolated and purified, but it may be, and preferably is, converted to the nitrophenoxyalkylchroman compound of formula (X) without intermediate isolation.

Conversion to the compound of formula (X) is effected by reacting the protected compound (IX) with a 4-halonitrobenzene in the presence of a base, such as sodium hydride, in a solvent, such as dimethyl sulfoxide or dimethylformamide. The amount of 4-halonitrobenzene employed is preferably about 2 moles per mole of protected compound (IX). The reaction temperature is preferably from 30° to 100° C. and the time required for the reaction is usually from several minutes to several hours.

Step (A3)

The nitro compound of formula (X) thus obtained is reduced in this step to the corresponding amino compound of formula (XI). In the course of or before or after this reduction, the protecting group R^7 may be allowed to remain as it is, removed or converted to another group (particularly an acryl group, such as an acetyl or benzoyl group).

When deprotection of the compound (X) is desired, this can easily be achieved by reacting the compound (X) with a dilute aqueous acid (such as hydrochloric acid, sulfuric acid or nitric acid) to hydrolyse the protecting group. The reaction is normally carried out in the presence of a solvent, for example: an alcohol, such as methanol, ethanol or propanol; an ether, such as tetrahydrofuran or dioxane; a ketone, such as acetone or methyl ethyl ketone; an organic acid, such as acetic acid or propionic acid; dimethyl sulfoxide; dimethylformamide; or water. Of these, water or an organic acid is preferred. The amount of acid used for hydrolysis is preferably from 0.01 to 5 moles, more preferably from 0.01 to 1 mole, per mole of the compound (X). We prefer to carry out the reaction in the presence of a large molar excess of water or of acetic acid as the solvent. The reaction temperature is preferably from ambient temperature to 100° C. and the time required for the reaction is normally from several minutes to about 20 hours.

If it is desired to convert the protecting group R^7 to another group, particularly an acyl group, this may be achieved by acylation of the deprotected compound obtained as described above. The acylating agent may be an acid halide, such as acetyl chloride or benzoyl chloride, or an acid anhydride, such as acetic anhydride. This reaction is preferably carried out in the presence of an organic amine (such as pyridine or triethylamine) or in the presence of an inorganic base (for example an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate or bicarbonate, such as sodium carbonate, potassium carbonate or sodium bicarbonate). The acylating reaction is preferably carried out in the presence of a solvent, for example: an aliphatic hydrocarbon, such as hexane, cyclohexane, heptane, ligroin or ethylcyclohexane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an organic amine, such as pyridine or triethylamine; a ketone, such as acetone or methyl ethyl ketone; an amide, such as dimethylformamide; a sulfoxide, such as dimethyl sulfoxide; or water. The ratio of the amount of deprotected compound (X) to acylating agent is not particularly critical, however, a slight molar excess of acylating agent is usually preferred, for example from 1 to 1.5 moles of acylating agent per mole of deprotected compound (X). Where an organic amine is employed as the acid-binding agent, it may be employed in any amount from 1 mole to a large molar excess per mole of the compound of formula (X). Where an inorganic base is employed as the acid-binding agent, it is preferably employed in an amount of from 1 to 10 moles per mole of the compound of formula (X). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the natures of the starting material and solvent employed, but the reaction is preferably effected at a temperature of from 0° to 100° C. for a period of from several minutes to 20 hours.

The nitro compound of formula (X) (which may optionally have been subjected to any of the processes described above) is then reduced to the amino compound of formula (XI). The reduction may be a catalytic reduction process employing hydrogen or reduction with a metal (such as zinc or iron) and an acid (which may be a mineral acid such as hydrochloric acid or sulfuric acid or an organic acid such as acetic acid). Preferably a catalytic reduction process is employed. The catalyst employed for this catalytic reduction is preferably palladium-on-carbon, Raney nickel or platinum oxide, of which palladium-on-carbon is particularly preferred. The hydrogen pressure is preferably from 1 to 100 atmospheres (1.01 to 101 bars), more preferably from 1 to 6 atmospheres (1.01 to 6.06 bars). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; water; or mixtures of any two or more thereof. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the nature of the starting material, the method employed for reduction and the solvent, but the reaction is normally effected at a temperature from ambient to 50° C. and the period required for the reaction is generally from several minutes to about 20 hours.

Step (A4)

The 2-(4-aminophenoxyalkyl)chroman derivative of formula (XI), prepared as described in step (A3) above, is diazotized and then subjected to a Meerwein arylation, to give the desired α-halocarboxylic acid compound of formula (IIa). The two reactions are preferably effected sequentially in the same reaction system and under essentially the same conditions.

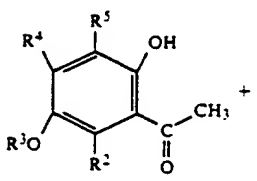
The diazotization reaction comprises reacting the amino compound of formula (IX) with a nitrite (such as sodium nitrite) in the presence of an acid, such as hydrochloric acid or hydrobromic acid.

The Meerwein arylation reaction comprises reacting the resulting diazonium compound with acrylic acid, an acrylic acid ester (such as methyl acrylate or ethyl acrylate) or another acrylic acid derivative (such as acrylonitrile or acrylamide) in the presence of a catalytic amount of a cuprous compound (which may be a salt, such as cuprous chloride, or another cuprous compound such as cuprous oxide). The acrylic acid esters are preferred and the preferred cuprous compound is cuprous oxide.

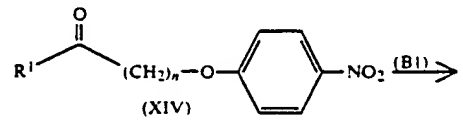
The reactions are preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reactions. Suitable solvents include: alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; water; or a mixture of any two or more thereof. The molar ratio of the amino compound of formula (XI) to the acrylic acid or derivative thereof is preferably from 1:1 to 1:15, more preferably from 1:5 to 1:10. The molar ratio of the amino compound (XI) to the cuprous compound is preferably from 1:0.01 to 1:1, more preferably from 1:0.03 to 1:0.3. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the natures of the starting materials and the solvent employed, but the reaction is normally carried out at a temperature from ambient temperature to 100° C., preferably from 30° to 60° C., and the period required for the reaction is normally from about 20 minutes to about 20 hours, more preferably from 30 minutes to 2 hours.

Method B

α-Halocarboxylic acid derivatives of formula (II) in which W represents a >C=O group, that is compounds of formula (IIb), may be prepared as illustrated in the following reaction scheme:

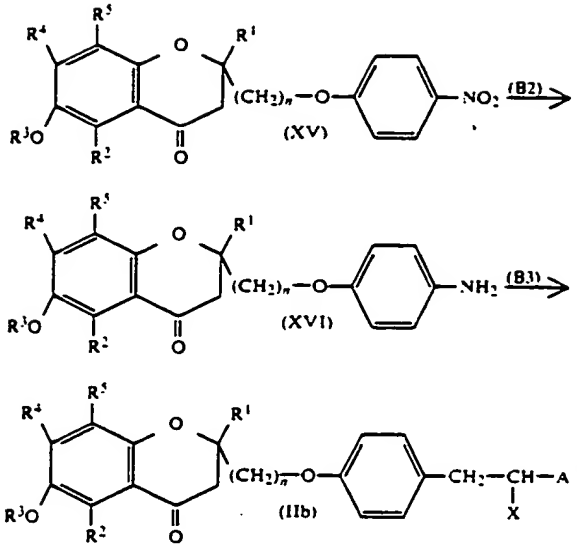


(XIII)



(XIV)

-continued



In the above formulae, R^1–R^5, n, A and X are as defined above. The reaction sequence comprises the following steps:

Step (B1)

The acetophenone derivative of formula (XIII) which is one of the starting materials for this step may be prepared, for example, as described in Chem. Berichte, 95, 1413. The other starting materials, the p-nitrophenoxyalkyl alkyl ketones of formula (XIV), may be prepared, for example, as described in J. Med. Chem., 21, 386 (1978) and J. Am. Chem. Soc., 99, 7653 (1977).

In this step, the compounds (XIII) or (XIV) are reacted together in the presence of a secondary amine, as described, for example, in Japanese Patent Application Kokai No. 19670/77.

The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: aliphatic and aromatic hydrocarbons, such as petroleum ether, benzene, toluene, xylene, hexane and cyclohexane; halogenated aliphatic and aromatic hydrocarbons, such as carbon tetrachloride, methylene chloride, chloroform, chlorobenzene and dichlorobenzene; ethers, such as diethyl ether, tetrahydrofuran and dioxane; amides, such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone; alcohols, such as methanol, ethanol and ethylene glycol monomethyl ether; esters, such as ethyl acetate; nitriles, such as acetonitrile; and sulfoxides, such as dimethyl sulfoxide.

The secondary amine employed in this reaction is preferably a compound of formula R^9—NH—R^{10}, in which R^9 and R^{10} may be the same or different and each represents an alkyl group or R^9 and R^{10}, together with the nitrogen atom to which they are attached, represent a nitrogen-containing heterocyclic ring system. Examples of such secondary amines include diethylamine, dimethylamine, N-methylpiperazine, pyrrolidine, piperidine or morpholine, of which pyrrolidine is particularly preferred.

The molar ratio of the compound of formula (XIII) to the compound of formula (XIV) is not particularly critical, but, to avoid waste, roughly equimolar amounts of the two compounds are used. In general, the amount of secondary amine is preferably from 0.05 to 1.5 moles, more preferably from 0.1 to 1 mole, per mole of the compound of formula (XIII) or (XIV).

The reaction conditions, particularly reaction temperature and time, may vary depending upon a number of factors, especially the nature of the starting materials and of the solvent, but, in general, we prefer to carry out the reaction at a temperature of from −30° C. to +150° C., more preferably from 10° to 120° C., for a period of from 30 minutes to 3 days.

Step (B2)

In this step, the nitro compound of formula (XV) prepared as in step (B1) is reduced to the corresponding amino compound of formula (XVI). This reaction is precisely the same as step (A3) of Method A, employing the same reaction conditions and reagents.

Step (B3)

In this step, the amino compound of formula (XVI), obtained as described in step (B2), is diazotized and then subjected to a Meerwein arylation, to give the desired α-halocarboxylic acid derivative of formula (IIb). These reactions are precisely the same as those described in step (A4) of Method A and may be carried out employing the same reagents and reaction conditions.

If desired, the corresponding α-halocarboxylic acid derivative of formula (II) in which W represents a >CH—OH or >CH—OR^6 group may be prepared following essentially the same procedures as described in steps (c) and (d) of the process of the present invention; it is, however, much preferred that, instead, the compound of formula (IIb) should be employed as the starting material in the process of the invention and that steps (c) and optionally (d) should be carried out, if desired, as part of the process of the invention.

The compounds of formulae (IIa) and (IIb) prepared as described above in Methods (A) and (B) can, if desired, be converted to various of their hydrolysis products or may be transesterified or converted to salts, for example such metal salts as the sodium, potassium, calcium or aluminum salts. Alternatively, they can be converted from metal salts or from compounds having free hydroxyphenyl groups or free carboxy groups to derivatives thereof, for example as follows:

Compounds in which R^3 represents a hydrogen atom and A represents a carboxy group can be prepared by hydrolysis of the corresponding compound of formula (II) in which, for example, R^3 represents an acyl group and A represents an alkoxycarbonyl group. This reaction is preferably effected in the presence of a base, for example: an inorganic base, such as an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate) of an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide); or an organic base, such as an alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide). The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: lower alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran or dioxane; water; or mixtures of any two or more thereof.

The molar ratio of the compound of formula (II) to the base is preferably from 1:1 to 1:5, more preferably

from 1:2 to 1:3. Although the reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the natures of the starting material, base and solvent employed, the reaction is generally carried out at a temperature of from −10° C. to +30° C., more preferably from 0° to 10° C. and the reaction time is generally from several minutes to several tens of hours.

The compound of formula (II) in which R^3 represents a hydrogen atom and A represents an alkoxycarbonyl group can be prepared by solvolysis of the corresponding compound in which R^3 represents an acyl group and A represents an alkoxycarbonyl group. This is carried out in the presence of a base, preferably an alkali metal alkoxide, such as sodium methoxide, sodium ethoxide or potassium t-butoxide. The reaction is preferably effected in the presence of a solvent, for example: an alcohol, such as methanol, ethanol, propanol, isopropanol or t-butanol; an ether, such as tetrahydrofuran or dioxane; or a mixture of any two or more thereof. If the alkoxycarbonyl group represented by A in the starting material is to be kept intact, it is preferred that the alkali metal alkoxide should be the alkoxide corresponding to this alkoxycarbonyl group and that the solvent should be an alcohol, which likewise corresponds to the alkoxycarbonyl group. However, the alkoxycarbonyl group in the starting material may, if desired, be converted into any other alkoxycarbonyl group by suitable choice of the alkali metal alkoxide and the alcohol solvent.

The molar ratio of the compound of formula (II) to the base is preferably from 1:1 to 1:3, more preferably from 1:1 to 1:2. The reaction conditions, especially the reaction temperature and reaction time, may vary, depending upon a number of factors, particularly the natures of the starting materials, bases and solvents employed, but the reaction is preferably carried out at a temperature of from −10° C. to +30° C., more preferably from 0° to 10° C., for a period of from several minutes to several tens of hours.

Compounds of formula (II) in which R^3 represents an acyl group and A represents a carboxy group may be prepared by hydrolysis of the corresponding compound of formula (II) in which R^3 represents an acyl group and A represents an alkoxycarbonyl group. In this case, the hydrolysis is effected in the presence of an inorganic base (for example an alkali metal carbonate, such as sodium carbonate or potassium carbonate, or an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide) or in the presence of another base such as an alkali metal alkoxide (for example sodium methoxide, sodium ethoxide or potassium t-butoxide). This reaction is preferably effected in the presence of a solvent, for example: a lower alcohol, such as methanol or ethanol; an ether, such as tetrahydrofuran or dioxane; water; or a mixture of any two or more thereof. The molar ratio of the compound of formula (II) to the base is preferably from 1:1 to 1:5, more preferably from 1:1 to 1:2. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, especially the natures of the starting materials, bases and solvents employed, but the reaction is normally effected at a temperature of from −10° C. to +30° C., more preferably from 0° to 10° C. for a period of from several minutes to several tens of hours.

In the α-halocarboxylic acid compounds of formula (II), the carbon atom at the 2-position of the chroman ring and that carbon atom to which the group A and the atom X are both attached are both asymmetric and accordingly give rise to stereoisomers, all of which are represented herein by a single formula. However, of course, the isomers may, if desired, be separated by conventional means and the present invention envisages the use of both individual isomers and mixtures thereof.

The α-halocarboxylic acid compounds of formula (II) have also been observed to lower the level of blood lipid peroxides and, in addition, have the effect of lowering blood triglycerides and blood cholesterol. They can therefore be expected to be useful as antihyperlipemic agents.

Of the compounds of formula (II) which exhibit the therapeutic effects mentioned above and which also form part of the present invention, preferred compounds are those listed below:

1. 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionic acid
2. 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionic acid
3. Ethyl 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionate
4. Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
5. Ethyl 3-[4-(6-benzoylozy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
6. 3-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionic acid
7. Ethyl 3-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
8. Ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
9. 2-chloro-3-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)phenyl]propionic acid
10. Ethyl 3-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
11. 2-chloro-3-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)phenyl]propionic acid
12. 3-{4-[2-(6-acetoxy-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]phenyl}-2-chloropropionic acid
13. Ethyl 2-bromo-3-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)phenyl]propionate
14. 2-chloro-3-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)phenyl]propionic acid
15. Ethyl 2-chloro-3-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)phenyl]propionate
16. Ethyl 3-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
17. Ammonium 2-chloro-3-{4-[2-(2-ethyl-6-hydroxy-5,7-diisopropylchroman-2-yl)ethoxy]phenyl}propionate
18. 3-{4-[6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-5,7-diisopropyl-2-methylchroman-2-ylmethoxy]phenyl}-2-chloropropionic acid
19. Sodium 2-chloro-3-{4-[3-(8-ethyl-5,7-diisopentyl-6-p-methylbenzoyloxy-2-propylchroman-2-yl)propoxy]phenyl}propionate
20. Potassium 2-chloro-3-{4-[2-(5,7-dibutyl-6-cyclohexanecarbonyloxy-2-isopropyl-8-propylchroman-2-yl)ethoxy]phenyl}propionate
21. Aluminum tris{3-[4-(2-butyl-6-2'-furoyloxy-7-isopentyl-5,8-dimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate}
22. 2-chloro-3-{4-[2-(2-isopentyl-5,7-dimethyl-6-phenylacetoxychroman-2-yl)ethoxy]phenyl}propionamide

23. Ethyl 3-[4-(6-acetoxy-2-ethyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
24. Ethyl 3-[4-(6-acetoxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate
25. 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]propionic acid
26. 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionic acid
27. Ethyl 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]propionate
28. Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
29. Ethyl 3-[4-(6-benzoyloxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
30. 3-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionic acid
31. Ethyl 3-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
32. Ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
33. 2-chloro-3-[4-(6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]propionic acid
34. Ethyl 3-[4-(6-acetoxy-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
35. 2-chloro-3-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-ylmethoxy)phenyl]propionic acid
36. 3-{4-[2-(6-acetoxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]phenyl}-2-chloropropionic acid
37. Ethyl 2-bromo-3-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)phenyl]-propionate
38. 2-chloro-3-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-ylmethoxy)phenyl]propionic acid
39. Ethyl 2-chloro-3-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-ylmethoxy)phenyl]propionate
40. Ethyl 3-[4-(6-acetoxy-2,7-dimethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate
41. Ammonium 2-chloro-3-{4-[2-(2-ethyl-6-hydroxy-5,7-diisopropyl-4-oxochroman-2-yl)ethoxy]phenyl}propionate
42. 2-chloro-3-{4-[6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-5,7-diisopropyl-2-methyl-4-oxochroman-2-ylmethoxy]phenyl}propionic acid
43. Sodium 2-chloro-3-{4-[3-(8-ethyl-5,7-diisopentyl-6-p-methylbenzoyloxy-4-oxo-2-propylchroman-2-yl)propoxy]phenyl}propionate
44. Potassium 2-chloro-3-{4-[2-(5,7-dibutyl-6-cyclohexanecarbonyloxy-2-isopropyl-4-oxo-8-propylchroman-2-yl)ethoxy]phenyl}propionate
45. Aluminum tris{3-[4-(2-butyl-6-2'-furoyloxy-7-isopentyl-5,8-dimethyl-4-oxochroman-2-ylmethoxy)-phenyl]-2-chloropropionate}
46. 2-chloro-3-{4-[2-(2-isopentyl-5,7-dimethyl-4-oxo-6-phenylacetoxychroman-2-yl)ethoxy]phenyl}propionamide
47. 2-chloro-3-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)phenyl]propionic acid

The compounds of the invention have been shown to have a very strong ability to lower the level of lipid peroxides, as demonstrated by the test against rat liver microsomal lipid peroxidation described in Biochem. Biophys. Res. Commun., 95, 734 (1980). In addition, in experiments using alloxan-induced hyperlipaemic mice, the compounds have demonstrated the ability to lower blood lipid peroxide, triglyceride and cholesterol levels. Moreover, the compounds of the invention are less toxic than many known compounds to experimental animals such as rats, as assessed by tests in which the appetite, body weight and hepatic enlargement are checked.

Accordingly, it is considered that the compounds of the present invention will be useful for the therapeutic treatment of human hyperlipaemia, diabetes and complications thereof, especially diabetes mellitus. The compounds of the invention may be administered orally, for example in the form of tablets, capsules, powders or granules, or parenterally, for example by injection or in the form of a suppository. The recommended dosage will, of course, vary depending upon the age and body weight of the patient as well as the nature and severity of the disease. However, for an adult human patient, a daily dose of from 50 mg to 5 g (which may be administered in a single dose or in divided doses) is recommended in the treatment of hyperlipaemia, diabetes mellitus and complications thereof.

The following Examples illustrate the preparation of various of the compounds of the present invention, whilst the subsequent Test Examples illustrate the valuable biological properties of these compounds. Preparation of various of the starting materials employed in the Examples is illustrated in the subsequent Preparations.

In the nuclear magnetic resonance spectra reported in the Examples and Preparations, the abbreviation "D" means that the signal disappeared upon the addition of heavy water (D_2O), and the abbreviation "nd" means that precise identification of the signal was not possible because of overlap by other signals or the absorption of the solvent.

EXAMPLE 1

(a)

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

A mixture of 9.6 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 1.8 g of thiourea and 11 ml of sulfolane was reacted for 80 minutes under a nitrogen stream at 115°-120° C. Subsequently, a mixture of 90 ml of acetic acid, 30 ml of concentrated hydrochloric acid and 15 ml of water was added to this, and the resulting mixture was further heated for 12 hours at 85°-90° C. 27 g of sodium bicarbonate were added to this reaction mixture, and, once evolution of carbon dioxide had ceased, the solvent was distilled off. A 10:1 by volume mixture of benzene and ethyl acetate was added to the residue, and the crude product was washed with a mixture of equal volumes of a saturated aqueous solution of sodium bicarbonate and water. The white powder produced was removed by filtration and washed again with water. It was then recrystallized from acetone to give 2.2 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one, melting at 205°-207° C.

Nuclear Magnetic Resonance Spectrum (heptadeuterated dimethylformamide + D_2O) δppm: 1.37 (3H, singlet); about 2 (2H, multiplet); 2.02 (3H, singlet); 2.14 (6H, singlet); 2.3-3.1 (solvent absorption); 3.42 (1H, doublet of doublets, J = 15 & 4.5 Hz); 4.60 (1H, doublet of doublets, J = 9 & 4.5 Hz); 6.93 (2H, doublet, J = 9 Hz); 7.23 (2H, doublet, J = 9 Hz).

(b)
5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

The organic solution produced by removing the white powder in step (a) above was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled off. The resulting crude product was purified by column chromatography through silica gel eluted with a mixture of benzene and ethyl acetate first in a volume ratio of 10:1 and then in a volume ratio of 10:1.4. 3.4 g of the desired 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, melting at 184°-186° C., were obtained from the fractions eluted with the latter mixture.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.39 (3H, singlet); about 2 (2H, multiplet); 2.02 (3H, singlet); 2.09 (3H, singlet); 2.13 (3H, singlet); 2.63 (2H, broad triplet, J=6 Hz); 3.07 (1H, doublet of doublets, J=15 & 9 Hz); 3.41 (1H, doublet of doublets, J=15 & 4.5 Hz); 3.97 (2H, AB Type, J=9 Hz); 4.70 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.90 (2H, doublet, J=9 Hz); 7.21 (2H, doublet, J=9 Hz).

EXAMPLE 2

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

3.1 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one [prepared as described in Example 1(a)] were added to a mixture of 45 ml of acetic acid, 15 ml of concentrated hydrochloric acid and 8 ml of water, and the mixture was reacted for 12 hours at 85°-90° C. It was then processed and purified in a similar manner to Example 1(a), giving 2.5 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, whose melting point and nuclear magnetic resonance spectrum were consistent with those of the product of Example 1(b).

EXAMPLE 3

(a) Benzene mono adduct of
5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

0.725 g of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione was dissolved in 4 ml of benzene; 400 mg of dry pyridine were added; 0.2 g of acetic anhydride was added dropwise under a nitrogen stream at 5°-10° C.; and the mixture was reacted for 2 days at room temperature. The resulting white crystals were separated by filtration, washed with benzene and vacuum-dried for 30 minutes at 90° C., giving 0.74 g of the benzene mono adduct of 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione. This substance was liquefied at 98°-100° C., solidified and again liquefied at 176°-178° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.42 (3H, singlet); 1.98 (3H, singlet); about 2 (2H, multiplet); 2.03 (3H, singlet); 2.09 (3H, singlet); 2.31 (3H, singlet); 2.63 (2H, broad triplet, J=6 Hz); 3.03 (1H, doublet of doublets, J=15 & 9 Hz); 3.42 (1H, doublet of doublets, J=15 & 4.5 Hz); 3.84 and 3.98 (2H, AB Type, J=9 Hz); 4.45 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.87 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 7.38 (6H, singlet); 8-8.5 (1H, broad singlet).

Elemental Analysis: Calculated for $C_{26}H_{29}NO_6S.C_6H_6$: C, 68.45%, H, 6.28%, N, 2.50%, S, 5.70%. Found: C, 68.54%, H, 6.13%, N, 2.51%, S, 5.87%.

(b)
5-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

In order that the desired free 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione could be obtained, 730 mg of the benzene mono adduct obtained as described in step (a) above were dissolved in 5 ml of acetone; the solvent was distilled off; the residue was solidified by adding water; and the white amorphous powder produced was vacuum-dried in a dessicator in the presence of phosphorus pentoxide, to give 0.61 g of the title compound, softening at about 90° C.

Elemental Analysis: Calculated for $C_{26}H_{29}NO_6S$: C, 64.60%, H, 6.06%, N, 2.90%, S, 6.62%. Found: C, 64.34%, H, 6.15%, N, 2.84%, S, 6.55%.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.41 (3H, singlet); 1.97 (3H, singlet); 1.98 (3H, singlet); about 2 (2H, nd); 2.04 (3H, singlet); 2.27 (3H, singlet); 2.67 (2H, broad triplet, J=6 Hz); 3.07 (1H, doublet of doublets, J=15 & 9 Hz); 3.42 (1H, doublet of doublets, J=15 & 4.5 Hz); 4.00 (2H, AB Type, J=9 Hz); 4.71 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.91 (2H, doublet, J=9 Hz); 7.21 (2H, doublet, J=9 Hz).

EXAMPLE 4

5-[4-(6-Acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

The procedure described in Example 1(a) was repeated, except that 490 mg of ethyl 3-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 100 mg of thiourea and 2 ml of sulfolane were heated at 110°-120° C. for 5 hours. The product was then treated as described in Example 1(a), except that the crude product (in the form of crystals) was washed with ethyl acetate, to give the title compound, softening at 228°-236° C.

Mass spectrum (m/e): 468 (M^+).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide+$CDCl_3$) δ ppm: 1.92 (3H, singlet); 1.93 (3H, singlet); 2.02 (3H, singlet); 1.63-2.17 (2H, nd); 2.30 (3H, singlet); 2.57-3.97 (4H, nd); 4.0-4.37 (3H, nd); 4.53 (1H, doublet of doublets, J=9 & 4 Hz); 6.93 (2H, doublet, J=9 Hz); 7.19 (2H, doublet, J=9 Hz); 8.5-9.0 (2H, broad singlet, D).

EXAMPLE 5

(a)
5-[4-(6-Acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione

The reactions described in Example 1(a) were repeated, except that 1.5 g of ethyl 3-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 300 mg of thiourea and 2 ml of sulfolane were heated at 120° C. for 2 hours. The reaction mixture was then purified by adding diethyl ether to the reaction mixture, and distilling off the solvent to leave a residue. This residue was purified by column chromatography through silica gel eluted first with a 9:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Mass spectrum (m/e): 455 (M^+).

Rf value: 0.41 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of benzene and ethyl acetate).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.42 (3H, singlet); 1.65–2.4 (2H, multiplet); 2.10 (3H, singlet); 2.28 (3H, singlet); 2.73 (2H, broad triplet, J=6 Hz); 3.0–3.6 (2H, multiplet); 3.93 (2H, AB Type, J=9 Hz); 4.50 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.70 (1H, singlet); 6.73 (1H, singlet); 6.85 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 8.7–9.0 (1H, broad singlet, D).

(b)

5-[4-(6-Acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

The silica gel chromatography column described in Example 5(a) was then eluted with a 1:4 by volume mixture of benzene and tetrahydrofuran, to give the title compound as a solid softening at 170°–175° C.

Rf value: 0.57 (thin layer chromatography, silica gel, developing solvent: 1:4 by volume mixture of benzene and tetrahyrofuran).

Mass spectrum (m/e): 454 (M^+).

Nuclear Magnetic Resonance Spectrum (heptadeuterated dimethylformamide) δ ppm: 1.39 (3H, singlet); 1.7–2.2 (2H, multiplet); 2.03 (3H, singlet); 2.27 (3H, singlet); 2.6–3.0 (3H, nd); 3.0–4.0 (1H, broad singlet, D); 3.42 (1H, doublet of doublets, J=15 & 4.5 Hz); 4.02 (2H, singlet); 4.53 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.65 (1H, singlet); 6.79 (1H, singlet); 6.95 (2H, doublet, J=9 Hz); 7.21 (2H, doublet, J=9 Hz); 8.4–9.0 (1H, broad singlet, D).

EXAMPLE 6

5-{4-[2-(6-Acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

The procedure described in Example 1(a) was repeated, except that 266 mg of ethyl 3-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]phenyl}-2-chloropropionate, 50 mg of thiourea and 4 ml of sulfolane were heated at 110°–120° C. for 4.5 hours. The product was treated as described in Example 1(a) except that the crude product was purified by column chromatography through silica gel eluted with a 1:1 by volume mixture of benzene and ethyl acetate, to give the title compound, melting at 175°–178° C.

Mass spectrum (m/e): 510 (M^+).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.24 (9H, singlet); 1.31 (3H, singlet); 1.82 (2H, broad triplet, J=7 Hz); 2.03 (2H, broad triplet, J=7 Hz); 2.25 (3H, singlet); 2.68 (2H, triplet, J=7 Hz); 2.87 (1H, doublet of doublets, J=14 & 9 Hz); 3.30 (1H, doublet of doublets, J=14 & 4 Hz); 4.13 (2H, triplet, J=7 Hz); 4.51 (1H, doublet of doublets, J=9 & 4 Hz); 6.68 (1H, singlet); 6.75 (1H, singlet); 6.87 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 8.67 (1H, broad singlet, D); 8.88 (1H, broad singlet, D).

EXAMPLE 7

5-{4-[2-(6-Acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

The procedure described in Example 1(a) was repeated, except that 558 mg of ethyl 3-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]-phenyl}-2-chloropropionate, 100 mg of thiourea and 12 ml of sulfolane were heated at 110°–115° C. for 3.5 hours. The product was subsequently treated as described in Example 1(a), except that the crude product, in the form of an oil, was purified by column chromatography through silica gel, eluted with a 20:1 by volume mixture of ethyl acetate and methanol, to give the title compound, softening at 103°–110° C.

Mass spectrum (m/e): 528 (M^+).

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.39 (3H, singlet); 1.94 (3H, singlet); 1.8–2.15 (4H, nd); 2.23 (3H, singlet); 2.63 (2H, broad triplet, J=6 Hz); 2.83 (1H, doublet of doublets, J=15 & 9 Hz); 3.42 (1H, doublet of doublets, J=15 & 5 Hz); 3.77 (3H, singlet); 3.78 (3H, singlet); 4.21 (2H, broad triplet, J=6 Hz); 4.45 (1H, doublet of doublets, J=9 & 5 Hz); 6.87 (2H, doublet, J=9 Hz); 7.19 (2H, doublet, J=9 Hz); 7.7–8.2 (1H, broad singlet, D).

EXAMPLE 8

5-{4-[2-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

1.6 g of ethyl 3-{4-[2-(6-acetoxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]phenyl}-2-chloropropionate, 300 mg of thiourea and 2 ml of sulfolane were heated at 110°–115° C. for 3 hours under a nitrogen stream. A mixture of 4 ml of water, 2 ml of ethylene glycol monomethyl ether and 1 ml of concentrated hydrochloric acid was then added and the whole mixture was heated at 95°–97° C. for 4.5 hours. The mixture was then treated as described in Example 1(a), except that the crude product, in the form of an oil, was purified by column chromatography through silica gel, eluted with a 10:1 by volume mixture of benzene and ethyl acetate, to give the title compound, melting at 152°–154° C.

Mass spectrum (m/e): 455 (M^+).

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.34 (3H, singlet); 1.87 (2H, broad triplet, J=7 Hz); 2.03 (3H, singlet); 2.07 (3H, singlet); 2.14 (3H, singlet); 2.0 (2H, nd); 2.64 (2H, broad triplet, J=7 Hz); 3.07 (1H, doublet of doublets, J=15 & 9 Hz); 3.41 (1H, doublet of doublets, J=15 & 4.5 Hz); 4.0–4.4 (3H, multiplet); 4.70 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.95 (2H, doublet, J=9 Hz); 7.20 (2H, doublet, J=9 Hz).

EXAMPLE 9

(a)

5-{4-[2-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

The procedure described in Example 1(a) was repeated, except that 13.5 g of ethyl 2-chloro-3-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]-phenyl}propionate, 4.4 g of thiourea and 20 ml of sulfolane were reacted for 14 hours at 110° C. The crude product was dissolved in ethyl acetate and the solution was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure and the resulting residue was purified by column chromatography through silica gel. This was first eluted with a 4:1 by volume mixture of benzene and ethyl acetate, and from these fractions were obtained the desired 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione, whose melting point and nuclear magnetic resonance spectra agreed with those of the product of Example 8.

(b)
5-{4-[2-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

The column described in Example 9(a) above was then eluted with a 1:1 by volume mixture of benzene and tetrahydrofuran, and from the resulting fractions were obtained the desired 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one, melting at 175°-180° C.

Mass spectrum (m/e): 454 (M^-).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.28 (3H, singlet); 1.6-2.2 (13H, nd); 2.2-3.2 (2H, nd); 2.80 (1H, doublet of doublets, J=15 & 9 Hz); 3.1-3.5 (1H, nd); 3.9-4.3 (2H, multiplet); 5.5 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.82 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 7.37 (1H, singlet, D); 8.67 (1H, broad singlet, D); 8.89 (1H, broad singlet, D).

EXAMPLE 10

5-[4-(6-Hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

290 mg of 5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one (prepared as described in Example 4) were added to a mixture of 3 ml of concentrated hydrochloric acid, 1.5 ml of water and 5 ml of ethylene glycol monomethyl ether, and the mixture was heated under reflux for 3.5 hours. The reaction mixture was then processed and purified as described in Example 1(a), and the crude product, in the form of an oil, was subjected to column chromatography through silica gel. The title compound, melting at 158°-159° C., was obtained from the fractions eluted with a 4:1 by volume mixture of benzene and ethyl acetate.

Mass spectrum (m/e): 427 (M^-).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.99 (3H, singlet); 2.04 (3H, singlet); 2.06 (3H, singlet); 1.5-2.25 (2H, nd); 2.25-2.87 (2H, nd); 2.87-3.5 (2H, nd); 3.97-4.34 (3H, nd); 4.87 (1H, doublet of doublets, J=9 & 4 Hz); 6.98 (2H, doublet, J=9 Hz); 7.20 (2H, doublet, J=9 Hz); 7.44 (1H, broad singlet, D); 11.3-12.3 (1H, broad singlet, D).

EXAMPLE 11

5-[4-(6-Hydroxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

170 mg of 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one (prepared as described in Example 5) were added to a mixture of 0.2 ml of 2N hydrochloric acid and 2 ml of ethylene glycol monomethyl ether, and the mixture was reacted at 95°-97° C. for 6 hours. It was then processed and purified as described in Example 1(a), except that the crude product, in the form of an oil, was subjected to column chromatography through silica gel, eluted with a 9:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value: 0.36 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 413 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.42 (3H, singlet); 1.78 (1H, doublet of doublets, J=15 & 7 Hz); 2.07 (1H, doublet of doublets, J=15 & 7 Hz); 2.17 (3H, singlet); 2.68 (2H, broad triplet, J=7 Hz); 3.06 (1H, doublet of doublets, J=15 & 9 Hz); 3.46 (1H, doublet of doublets, J=15 & 4.5 Hz); 3.88 (2H, AB Type, J=9 Hz); 4.4-4.6 (2H, multiplet), changing after adding D_2O to 4.47 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.50 (1H, singlet); 6.62 (1H, singlet); 6.87 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 8.4-8.6 (1H, broad singlet, D).

EXAMPLE 12

5-{4-[2-(7-t-Butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

75 mg of 5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one (prepared as described in Example 6) were added to a mixture of 0.5 ml of concentrated hydrochloric acid, 2 ml of water and 2 ml of ethylene glycol monomethyl ether, and the mixture was heated under reflux for 4 hours. The mixture was then processed and purified by the procedures described in Example 1(a), except that the crude product, in the form of an oil, was purified by column chromatography through silica gel, eluted with a 5:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value: 0.21 (thin layer chromatography, silica gel, developing solvent: 5:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 469 (M^-).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.30 (9H, singlet); 1.32 (3H, singlet); 1.77 (2H, broad triplet, J=7 Hz); 1.99 (2H, broad triplet, J=7 Hz); 2.60 (2H, broad triplet, J=7 Hz); 3.03 (1H, doublet of doublets, J=15 & 9 Hz); 3.29 (1H, doublet of doublets, J=15 & 4.5 Hz); 4.11 (2H, broad triplet, J=7 Hz); 4.85 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.48 (1H, singlet); 6.51 (1H, singlet); 6.89 (2H, doublet, J=9 Hz); 7.16 (2H, doublet, J=9 Hz); 8.63 (1H, broad singlet, D); 11.3-12.7 (1H, broad singlet, D).

EXAMPLE 13

5-{4-[2-(6-Hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]-benzyl}thiazolidine-2,4-dione

560 mg of 5-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one (prepared as described in Example 7) were added to a mixture of 7 ml of concentrated hydrochloric acid, 2.5 ml of water and 10 ml of ethylene glycol monomethyl ether, and the mixture was heated under reflux for 13 hours. The reaction mixture was then processed and purified as described in Example 1(a), except that the crude product, in the form of an oil, was purified by column chromatography through silica gel eluted with a 9:1 by volume mixture of chloroform and ethyl acetate, to give the title compound.

Rf value: 0.15 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of chloroform and ethyl acetate).

Mass spectrum (m/e): 487 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.39 (3H, singlet); 1.90 (2H, broad triplet, J=6 Hz); 2.10 (3H, singlet); 2.15 (2H, broad triplet, J=6 Hz); 2.62 (2H, broad triplet, J=6 Hz); 3.09 (1H, doublet of doublets, J=15 & 9 Hz); 3.45 (1H, doublet of doublets, J=15 & 5 Hz); 3.85 (3H, singlet); 3.95 (3H, singlet); 4.20 (2H, broad triplet, J=6 Hz); 4.49 (1H, doublet of doublets, J=9 & 5 Hz); 5.40 (1H, singlet, D); 6.87 (2H,

doublet, J=9 Hz); 7.16 (2H, doublet, J=9 Hz); 8.1–8.4 (1H, broad singlet, D).

EXAMPLE 14

5-{4-[2-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

The reaction described in Example 13 was repeated, except that 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one (prepared as described in Example 9) was used as the starting material. This was subsequently treated as described in Example 1(a) and then separated and purified as in Example 8, to give the title compound, whose melting point and mass and nuclear magnetic resonance spectra agreed with those of the product of Example 8.

EXAMPLES 15–18

The procedure described in Example 3 was repeated, except that the acetic anhydride was replaced by the appropriate acylating agent identified hereafter and, in Example 18, a different thiazolidine derivative was used, to give the following compounds:

EXAMPLE 15

5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, using butyryl chloride

Melting at: 147°–150° C.

Mass spectrum (m/e): 511 (M^-).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.06 (3H, triplet, J=6 Hz); 1.65–2.2 (13H, multiplet); 2.45–2.75 (4H, multiplet).

EXAMPLE 16

5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, from benzoic anhydride.

Rf value: 0.53 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 545 (M^+).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 7.45–7.85 (3H, multiplet); 8.05–8.3 (2H, multiplet).

EXAMPLE 17

5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, from nicotinoyl chloride hydrochloride

Melting at: 196°–198° C.

Mass spectrum (m/e): 546 (M^-).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 7.35–7.65 (1H, multiplet); 8.43–8.65 (1H, multiplet); 8.7–9.1 (1H, multiplet); 9.4–9.6 (1H, multiplet).

EXAMPLE 18

5-{4-[2-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione, from nicotinoyl chloride hydrochloride and 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (prepared as described in Example 14)

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 1:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 560 (M^+).

Nuclear Magnetic Resonance Spectrum (heptadeuterated dimethylformamide) δ ppm: 7.6–7.85 (1H, multiplet); 8.5–8.7 (1H, multiplet); 8.9–9.1 (1H, multiplet); 9.35–9.5 (1H, multiplet).

In the nuclear magnetic resonance spectra reported in the above Examples 15–18, only those signals are reported which are characteristic of the 6-acyloxy part of the compound prepared.

EXAMPLE 19

5-[4-(2-Ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

2.4 g of ethyl 3-[4-(6-acetoxy-2-ethyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 494 mg of thiourea and 3 ml of sulfolane were heated under a nitrogen stream for 4.5 hours at 100°–110° C. At the end of this time, 3 ml of ethylene glycol monomethyl ether, 3 ml of water and 1 ml of concentrated hydrochloric acid were added and the resulting mixture was heated for a further 3.5 hours at 96°–98° C. The reaction mixture was then processed as described in Example 1(a) and the resulting crude product, in the form of an oil, was purified by column chromatography, eluted with a 10:1 by volume mixture of benzene and ethyl acetate, to give the title compound.

Rf value: 0.29 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 455 (M^-).

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 0.90 (3H, triplet, J=6 Hz); 1.5–2.1 (4H, nd); 1.99 (3H, singlet); 2.01 (3H, singlet); 2.05 (3H, singlet); 2.4–2.7 (2H, multiplet); 2.8–3.7 (2H, nd); 3.94 (2H, singlet); 4.84 (1H, doublet of doublets, J=9 & 4.5 Hz); 6.90 (2H, doublet, J=9 Hz); 7.15 (2H, doublet, J=9 Hz); 7.40 (1H, broad singlet, D).

EXAMPLE 20

5-[4-(6-Hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

1.99 g of ethyl 3-[4-(6-acetoxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 0.42 g of thiourea and 2.1 g of sulfolane were reacted under a nitrogen stream at 125°–150° C. for 3.5 hours. At the end of this time, 15 ml of ethylene glycol monomethyl ether, 4 ml of water and 2 ml of concentrated hydrochloric acid were added and the mixture was reacted for a further 3.5 hours at 96°–98° C. The reaction mixture was then treated as described in Example 1(a) and the resulting crude product, in the form of an oil, was purified by column chromatography through silica gel, eluted with a 5:1 by volume mixture of hexane and ethyl acetate, to give the title compound.

Rf value: 0.30 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 483 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.96 (3H, doublet, J=6 Hz); 1.01 (3H, doublet, J=6 Hz); 1.71 (2H, doublet, J=6 Hz); 1.8–2.3 (3H, nd); 2.10 (6H, singlet); 2.16 (3H, singlet); 2.61 (2H, triplet, J=6 Hz); 3.02 (1H, doublet of doublets, J=9 & 15 Hz); 3.43 (1H, doublet of doublets, J=4 & 15 Hz); 3.92 (2H, singlet); 4.33 (1H, singlet); 4.43 (1H, doublet of doublets, J=4 & 9 Hz); 6.85 (2H, doublet, J=9 Hz); 7.13 (2H, doublet, J=9 Hz); 8.4–9.0 (1H, broad).

EXAMPLE 21

Monosodium salt of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

101 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione were suspended in 0.5 ml of 99.5% ethanol. 4.33 ml of a 0.0526N ethanolic solution of sodium hydroxide were then added to the suspension and the mixture was stirred at room temperature for 1 hour. The crystals obtained by evaporating off the solvent under reduced pressure were dried by heating them under reduced pressure at 60° C. for 3 hours in the presence of phosphorus pentoxide, to give the title compound, melting at 203°-208° C. (with decomposition).

Nucelar Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.30 (3H, singlet); 1.66-2.10 (2H, multiplet); 1.96 (3H, singlet); 2.03 (3H, singlet); 2.05 (3H, singlet); 2.35-2.80 (3H, multiplet); 3.15-3.35 (1H, multiplet); 3.92 (2H, broad singlet); 4.09 (1H, doublet of doublets, J=4.5 & 11.5 Hz); 6.85 (2H, doublet, J=9 Hz); 7.10 (2H, doublet, J=9 Hz); 7.42 (1H, broad singlet, D).

Elemental analysis: Calculated for $C_{24}H_{26}NO_5SNa.H_2O$: C, 59.86%; H, 5.86%; N, 2.91%; S, 6.66%; Na, 4.77%. Found: C, 59.78%; H, 5.54%; N, 2.84%; S, 6.37%; Na, 5.04%.

EXAMPLE 22

5-[4-(6-Hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

A mixture of 1.3 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 45), 0.4 g of thiourea and 2 g of sulfolane was heated at 120°-130° C. for 4 hours under a nitrogen stream. Then 15 ml of ethylene glycol monomethyl ether, 4 ml of water and 2 ml of concentrated hydrochloric acid were added, in that order, to the reaction mixture, and heating was continued, but at 70°-90° C., for a further 2.5 days. Water was then added to the reaction mixture, after which it was extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate. Benzene was distilled off from the extract. The residue was subjected to silica gel column chromatography, eluted with a 5:3 by volume mixture of hexane and ethyl acetate, to yield 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione. Its softening point was 79°-83° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.50 (3H, singlet); 2.11 (3H, singlet); 2.22 (3H, singlet); 2.56 (3H, singlet); 2.66 (1H, doublet, J=15 Hz); 3.05 (1H, doublet, J=15 Hz); 3.05 (1H, doublet of doublets, J=9 & 15 Hz); 3.42 (1H, doublet of doublets, J=4 & 15 Hz); 3.95 (1H, doublet, J=10 Hz); 4.07 (1H, doublet, J=10 Hz); 4.46 (1H, doublet of doublets, J=4 & 9 Hz); 4.5-5.2 (1H, broad singlet); 6.84 (2H, doublet, J=9 Hz); 7.13 (2H, doublet, J=9 Hz).

EXAMPLE 23

5-[4-(4,6-Dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

450 mg of sodium borohydride were added to a mixture of 278 mg of 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (prepared as described in Example 22) and 9 ml of methanol, and the resulting mixture was stirred at room temperature for 2 hours. Then, a 1% w/v aqueous solution of acetic acid was added to the reaction mixture, and the mixture was neutralized with an aqueous solution of potassium carbonate and extracted with ethyl acetate. The ethyl acetate solution was washed with water and dried over anhydrous sodium sulfate. Ethyl acetate was distilled off from the mixture under reduced pressure, and the resulting residue was subjected to silica gel column chromatography, eluted with a 5:3 by volume mixture of hexane and ethyl acetate, to yield 5-[4-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione. Its melting point was 102°-118° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone and D_2O) δ ppm: 1.52 (3H, singlet); 2.01 (3H, singlet); 2.13 (3H, singlet); 2.29 (3H, singlet); 1.9-2.5 (1H, nd); 2.9-3.6 (2H, multiplet); 4.03 (2H, singlet); 3.9-4.5 (1H, nd); 4.6-5.1 (2H, multiplet); 6.7-7.4 (4H, nd).

EXAMPLE 24

5-[4-(7-t-Butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

In a similar manner to Example 22, a mixture of 291 mg of ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 49), 64 mg of thiourea and 1 ml of sulfolane was heated. 5 ml of ethylene glycol monomethyl ether, 1 ml of concentrated hydrochloric acid and 2 ml of water were added, and the resulting mixture was further heated under reflux for 6 hours. Ethyl acetate was then added to the reaction mixture, and the resulting solution was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate was removed by evaporation under reduced pressure, and the resulting residue was subjected to silica gel column chromatography, eluted with a 5:1 by volume mixture of benzene and ethyl acetate, to give 143 mg of the desired 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione.

Softening point: 95°-107° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.40 (9H, singlet); 1.48 (3H, singlet); 2.65 (1H, doublet, J=16.5 Hz); 3.05 (1H, doublet, J=16.5 Hz); 3.08 (1H, doublet of doublets, J=9 & 14 Hz); 3.42 (1H, doublet or doublets, J=4.5 & 14 Hz); 4.14 (2H, singlet); 4.74 (1H, doublet of doublets, J=4.5 & 9 Hz); 6.83 (1H, singlet); 6.92 (2H, doublet, J=9 Hz); 7.23 (1H, singlet); 7.24 (2H, doublet, J=9 Hz); 7.50-9.40 (1H, broad, D).

EXAMPLE 25

5-[4-(6-Acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

A mixture of 2.0 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate (prepared as described in Preparation 45), 0.62 g of thiourea, and 3.1 g of sulfolane was heated at 120°-125° C. for 7 hours under a nitrogen stream. The reaction mixture was extracted with benzene and then the benzene was distilled off from the extract. Water was then added to the residue and the oily layer was separated. The oily layer was subjected to silica gel column chromatography [successively with an eluent of

(1) a 2:1 by volume mixture of n-hexane and ethyl acetate, (2) ethyl acetate, and (3) a 1:1 by volume mixture of ethyl acetate and ethanol] to yield 5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one in a yield of 0.74 g. This was further purified by recrystallization from ethyl acetate, to give the purified title compound melting at was 218°-222° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide + D_2O) δ ppm: 1.43 (3H, singlet); 2.04 (6H, singlet); 2.32 (3H, singlet); 2.35 (3H, singlet); 2.4-3.5 (4H, nd); 4.13 (2H, singlet); 4.56 (1H, doublet of doublets, J=4 & 9 Hz); 6.85 (2H, doublet, J=9 Hz); 7.14 (2H, doublet, J=9 Hz).

TEST EXAMPLE 1

Effect on hyperlipidaemia

The test animals were 8 weeks old male mice. These animals were fasted for 18 hours, after which 75 mg/kg of alloxan was injected into the tail vein of each animal. Each of the test compounds was administered orally at a dose of 100 mg/kg body weight 30 minutes before and 24 and 30 hours after administration of the alloxan. Blood was collected from an incision in the cervical region 48 hours after administration of the alloxan. The amount collected was 100 or 200 μl. The blood was diluted 10 or 20 times with a physiological saline solution and centrifuged (3,000 rpm, 10 minutes) to determine the lipid content.

Lipid peroxide was determined at TBA (thiobarbituric acid)—reacting substance according to Yagi's method [K. Yagi: Biochem. Med., 15, 212-216 (1976)]. Measurements of cholesterol and triglyceride were made according to the enzyme method. A Determiner TC (a registered trade mark of Kyowa Medix) kit was used for the measurement of cholesterol and Triglyceride Measuring Agent (GPO-p-chlorophenol color developing method) (Wako Jyunyaku) kit was used for triglyceride.

As a control, the procedure was repeated, except that no test compound was administered.

The test compounds were as follows:

Compound A:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (a compound of the invention);

Compound B:

5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (a prior art compound).

The results are shown in the following Table:

TABLE 1

agent	No. of animals	lipid peroxide (nmol/ml)	triglyceride (mg/dl)	cholesterol (mg/dl)
Control	10	36.8 ± 6.9	636 ± 128	81.3 ± 4.7
Compound A	10	16.8 ± 1.5 ($P < 0.02$)	270 ± 33 ($P < 0.02$)	59.6 ± 1.4 ($P < 0.01$)
Compound B	10	29.9 ± 5.2 (NS)	586 ± 127 (NS)	72.5 ± 5.6 (NS)

NS = not significant.

As shown in Table 1, Compound A of this invention significantly inhibited lipid peroxide, triglyceride and cholesterol, but the comparative compound did not exhibit such an inhibitory action.

TEST EXAMPLE 2

Effect On Blood Sugar

The test animals employed were male mice of the $C_{57}BL/6J$-Ob/Ob strain aged about 4 months. The animals were employed in groups of 4 for each test.

Compound A and the same prior art Compound B as was used in Test Example 1 were mixed at a level of 0.2% by weight with a powder feed (MM-1, Funabashi Farm) and given freely to the mice for 2 weeks, during which time water was also freely available. At the end of the experiment, blood was collected from a vein in the tail and the blood sugar level was determined by the glucose oxidase method. A control group was treated similarly, except that the active compounds were omitted.

With the blood sugar level of the control set arbitrarily at 100, the blood sugar level of Compound A was 57 and that of Compound B was 56, indicating an excellent ability to reduce blood sugar levels.

PREPARATION 1

6-(Methoxymethoxy)-2,5,7,8-tetramethylchroman-2-ylmethanol

16.1 g of 6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethanol were dissolved in 70 ml of dry dimethylformamide. 3.0 g of a 50% w/w suspension of sodium hydride in oil (which had been washed with cyclohexane 3 times) were added gradually to the resulting solution at 5°-10° C., with stirring and under a nitrogen stream. The mixture was reacted for 1 hour at room temperature, and then the solution was ice-cooled to 3°-5° C., and 5.5 g of chloromethyl methyl ether dissolved in 40 ml of dry benzene were added dropwise. After the whole of this had been added, the solution was reacted for 1 hour at room temperature. The reaction mixture was then poured into ice-water and extracted with cyclohexane. The extract was washed four times with a 5% w/v aqueous solution of sodium hydroxide, and then with water. It was then dried and the solvent was distilled off under reduced pressure, giving the desired 6-(methoxymethoxy)-2,5,7,8-tetramethylchroman-2-ylmethanol. On thin layer chromatography, the Rf value was 0.45 [silica gel; developing solvent:benzene:ethyl acetate=4:1 by volume].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.21 (3H, singlet); 1.6-2.0 (3H, multiplet); 2.07 (3H, singlet); 2.15 (3H, singlet); 2.19 (3H, singlet); 2.6 (2H, broad triplet, J=9 Hz); 3.60 (3H, singlet); 3.63 (2H, singlet); 4.85 (2H, singlet).

PREPARATION 2

6-(Methoxymethoxy)-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman

6 g of a 50% w/w suspension of sodium hydride in oil were placed in a reaction container and washed with cyclohexane. 100 ml of dry dimethyl sulfoxide and then 19.0 g of 6-(methoxymethoxy)-2,5,7,8-tetramethylchroman-2-ylmethanol dissolved in 20 ml of dry benzene were added, and the mixture was reacted for 20 minutes under a nitrogen stream at 60° C. Small portions of p-chloronitrobenzene (totalling 21.6 g) were added to this solution whilst cooling with water to 30° C., and then the reaction was continued for 1 hour at 60° C. The reaction mixture was then poured into ice-water and extracted with ethyl acetate. The extract was washed

with water, and dried over anhydrous sodium sulfate. The solvent was distilled off, leaving a reddish brown crude oil. This oil was subjected to silica gel column chromatography, eluted first with a 1:1 by volume mixture of benzene and cyclohexane and then with benzene alone. A light yellowish oil, the desired 6-(methoxymethoxy)-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)-chroman, was obtained from the portion eluted with benzene. Rf value on thin layer chromatography: 0.12 [silica gel; developing solvent:benzene].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.41 (3H, singlet); about 2 (2H, multiplet); 2.05 (3H, singlet); 2.14 (3H, singlet); 2.18 (3H, singlet); 2.6 (2H, broad triplet, J=9 Hz); 3.60 (3H, singlet); 3.95 and 4.09 (2H, AB type, J=9 Hz); 4.86 (2H, singlet); 6.96 (2H, doublet, J=9 Hz); 8.19 (2H, doublet, J=9 Hz).

PREPARATION 3

6-Hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman

32.8 g of 6-(methoxymethoxy)-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman were dissolved in 300 ml of acetic acid containing 5.3 g of a 10% w/w aqueous solution of sulfuric acid, and the mixture was heated for 10 minutes at 60° C. The reaction mixture was cooled and then poured into a mixture of 420 g of sodium bicarbonate and 1 kg of ice and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off from the extract, leaving a light yellowish powder, the desired 6-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman, melting at 114°–116° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.41 (3H, singlet); about 2 (2H, multiplet); 2.06 (3H, singlet); 2.10 (3H, singlet); 2.15 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 4.05 (2H, AB Type, J=9 Hz); 4.25 (1H, broad singlet); 6.96 (2H, doublet, J=9 Hz); 8.16 (2H, doublet, J=9 Hz).

PREPARATION 4

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman

20.4 g of 6-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman were dissolved in 60 ml of pyridine, and, while stirring, 30 ml of acetic anhydride were added dropwise at 10° C. The mixture was gradually restored to room temperature and then reacted for 1 hour at 30° C. The reaction mixture was cooled and then poured into ice-water and extracted with a 1:1 by volume mixture of benzene and cyclohexane. The extract was washed well with a 2% w/v aqueous solution of hydrochloric acid and then with water, after which it was dried over anhydrous sodium sulfate. The solvent was removed by evaporation under reduced pressure, giving the desired 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman. Rf value on thin layer chromatography: 0.64 [silica gel; developing solvent; benzene and ethyl acetate=10:1 by volume]

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.41 (3H, singlet); 1.98 (3H, singlet); about 2 (2H, multiplet); 2.02 (3H, singlet); 2.05 (3H, singlet); 2.31 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 3.98 and 4.10 (2H, AB Type, J=9 Hz); 6.97 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 5

6-Acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman

24.3 g of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman were dissolved in a mixture of 200 ml of methanol and 20 ml of benzene and reacted for 3 hours under a hydrogen pressure of 45–55 lb/sq. inch (3.1–3.8 bars), using Pearl's hydrogen adding apparatus, in the presence of 7 g of 10% w/w palladium-on-carbon. The palladium-on-carbon was removed by filtration from the reaction mixture and washed with a mixture of 600 ml of acetone and 60 ml of concentrated hydrochloric acid. The filtrate and the washings were combined and the mixture was neutralized with sodium bicarbonate. The solvent was then distilled off, and the crude crystals obtained were dissolved in ethyl acetate. The ethyl acetate solution was washed with water and dried over anhydrous sodium sulfate. The ethyl acetate was then distilled from the extract, and the crude substance obtained was washed with a 1:1 by volume mixture of benzene and cyclohexane, giving the desired 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman, melting at 138°–140° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.42 (3H, singlet); about 2 (2H, multiplet); 2.00 (3H, singlet); 2.04 (3H, singlet); 2.10 (3H, singlet); 2.31 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 3.37 (2H, broad singlet); 3.80 and 3.95 (2H, AB Type, J=9 Hz); 6.62 (2H, doublet, J=9 Hz); 6.78 (2H, doublet, J=9 Hz).

PREPARATION 6

Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate

17.5 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman were dissolved in a mixture of 130 ml of acetone and 30 ml of water, and 13 ml of concentrated hydrochloric acid, followed by 4.3 g of sodium nitrite dissolved in 8.5 ml of water, were added dropwise, with ice-cooling, to the product. 37.3 ml of ethyl acrylate were added dropwise, and then 680 mg of cuprous oxide were added gradually to the product, whilst keeping its temperature at 40°–43° C. Generation of nitrogen terminated after about 30 minutes. Benzene was then added to the reaction mixture (which consisted of 2 layers) to extract the organic layer. The benzene extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was then distilled off from the extract. The dark brownish oil thus obtained was subjected to silica gel column chromatography, eluted with a 1:1 by volume mixture of benzene and cyclohexane and then the proportion of benzene was progressively increased until it was eluted with benzene alone. Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate was obtained from the fractions eluted with a 2:1 by volume mixture of benzene and cyclohexane and with benzene alone. Rf value on thin layer chromatography: 0.39 [silica gel; developing solvent:benzene:ethyl acetate=20:1 by volume].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.23 (3H, triplet, J=7.5 Hz); 1.42 (3H, singlet); 1.98 (3H, singlet); about 2 (2H, multiplet); 2.04 (3H, singlet); 2.09 (3H, singlet); 2.31 (3H, singlet); 2.6 (2H,

broad triplet, J=6 Hz); 3.05 (1H, doublet or doublets, J=15 & 7.5 Hz); 3.31 (1H, doublet or doublets, J=15 & 7.5 Hz); 3.83 and 3.99 (2H, AB Type, J=9 Hz); 4.18 (2H, quartet, J=7.5 Hz); 4.38 (1H, triplet, J=7.5 Hz); 6.85 (2H, doublet, J=9 Hz); 7.14 (2H, doublet, J=9 Hz).

PREPARATION 7

3-[4-(6-Acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionic acid

0.16 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate was dissolved in a mixture of 1.5 ml of 99.5% ethanol and 0.2 ml of tetrahydrofuran. 265 mg of a 9.55% w/w aqueous solution of sodium hydroxide were added dropwise, under a nitrogen stream at 0°–4° C., to the resulting mixture. The mixture was then reacted for a further 20 hours at 0°–5° C., after which it was neutralized, whilst ice-cooling, by adding 0.68 g of a 10% w/w aqueous solution of hydrochloric acid. The solvent was then distilled off under reduced pressure. The separated light reddish oil was further extracted with chloroform, and the chloroform extract was washed with water and dried over anhydrous sodium sulfate. The crude product obtained by distilling off the chloroform under reduced pressure was subjected to column chromatography through silica gel and the desired 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionic acid was obtained from the fractions eluted with a 20:1 by volume mixture of benzene and 99.5% ethanol. Rf value on thin layer chromatography: 0.6 (tailing) [silica gel; developing solvent; benzene:99.5% ethanol=4:1 by volume].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.42 (3H, singlet); 1.98 (3H, singlet); about 2 (2H, multiplet); 2.03 (3H, singlet); 2.09 (3H, singlet); 2.32 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 3.2 (2H, multiplet); 3.85 and 4.00 (2H, AB Type, J=9 Hz); 4.4 (1H, multiplet); 6.86 (2H, doublet, J=9 Hz); about 7 (1H, broad singlet); 7.15 (2H, doublet, J=9 Hz).

PREPARATION 8

2-Chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionic acid

0.48 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate was dissolved in a mixture of 5 ml of 99.5% ethanol and 2 ml of tetrahydrofuran. To this was added dropwise, under a nitrogen stream at 8°–10° C., a solution prepared by dissolving 133 mg of sodium hydroxide in 1 ml of 99.5% ethanol. When the whole of the solution had been added, the mixture was reacted for a further 18 hours at 0°–5° C., after which it was neutralized by adding to it dropwise a solution prepared by dissolving 0.37 g of concentrated hydrochloric acid in 1 ml of 99.5% ethanol. The solvent was then distilled off from the mixture under reduced pressure. The pale reddish oil thus separated was extracted with chloroform, and the chloroform extract was washed with water and then dried over anhydrous sodium sulfate. The crude product obtained by distilling the chloroform off under reduced pressure was subjected to silica gel column chromatography, and the desired 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionic acid was obtained from the fractions eluted with a 10:1 by volume mixture of benzene and ethyl acetate. Rf value on thin layer chromatography: 0.4 (tailing) [silica gel; developing solvent; benzene:99.5% ethanol=6:1 by volume]. Melting point 148°–149° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δppm: 1.40 (3H, singlet); about 2 (2H, multiplet); 2.10 (6H, singlet); 2.15 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 3.05 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.30 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.83 and 3.98 (2H, AB type, J=9 Hz); 4.40 (1H, triplet, J=7.5 Hz); about 6 (2H, broad singlet); 6.85 (2H, doublet, J=9 Hz); 7.14 (2H, doublet, J=9 Hz).

PREPARATION 9

Ethyl 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionate

0.48 g of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate was dissolved in a mixture of 3 ml of absolute ethanol and 2 ml of dry tetrahydrofuran. An ethanolic solution of sodium ethoxide (prepared by dissolving 49.0 mg sodium in 2 ml of absolute ethanol) was added dropwise, under a nitrogen stream at 10°–13° C., to the resulting solution. The mixture was then reacted for 21 hours at 0°–5° C., after which 0.22 g of concentrated hydrochloric acid dissolved in 99.5% ethanol was added dropwise, with ice-cooling. The solvent was then distilled off from the reaction mixture under reduced pressure; the separated light reddish oil was extracted with chloroform; and the extract was washed with water and then dried over anhydrous sodium sulfate. The crude product obtained by distilling the chloroform off from the extract under reduced pressure was subjected to silica gel column chromatography, and the desired ethyl 2-chloro-3-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]propionate was obtained from the fractions eluted with benzene. Rf value on thin layer chromatography: 0.60 [silica gel; developing solvent; benzene:ethyl acetate=10:1 by volume].

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.23 (3H, triplet, J=7.5 Hz); 1.40 (3H, singlet); about 2 (2H, multiplet); 2.10 (6H, singlet); 2.15 (3H, singlet); 2.6 (2H, broad triplet, J=6 Hz); 3.05 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.30 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.83 and 3.95 (2H, AB Type, J=9 Hz); 4.16 (2H, quartet, J=7.5 Hz); 4.18 (1H, singlet); 4.36 (1H, triplet, J=7.5 Hz); 6.85 (2H, doublet, J=9 Hz), 7.13 (2H, doublet, J=9 Hz).

In the following Preparations 10–38, only those parts of the signals of the nuclear magnetic resonance spectra which are relevant to the compounds prepared are reported.

PREPARATIONS 10–16

The procedure described in Preparation 3 was repeated, but using the appropriate chroman starting material, to prepare the following compounds:

PREPARATION 10

6-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-chroman

Melting at: 167.5°–169° C.

Mass spectrum (m/e): 343 (M^+).

Rf value: 0.60 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.23 (1H, singlet, D); 7.05 (2H, doublet, J=9 Hz); 8.23 (2H, doublet, J=9 Hz).

PREPARATION 11

6-hydroxy-2,7-dimethyl-2-(4-nitrophenoxymethyl)-chroman

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 329 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.03 (1H, singlet, D); 6.95 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 12

7-t-butyl-6-hydroxy-2-methyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Rf value: 0.71 (thin layer chromatography, silica gel, developing solvent: 5:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 385 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.34 (1H, singlet, D); 6.97 (2H, doublet, J=9 Hz); 8.21 (2H, doublet, J=9 Hz).

PREPARATION 13

6-hydroxy-7,8-dimethoxy-2,5-dimethyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Melting at: 119°-121° C.

Mass spectrum (m/e): 403 (M^+).

Rf value: 0.49 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 5.43 (1H, singlet, D); 6.99 (2H, doublet, J=9 Hz); 8.23 (2H, doublet, J=9 Hz).

PREPARATION 14

6-hydroxy-2,5,7,8-tetramethyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Rf value: 0.33 (thin layer chromatography, silica gel, developing solvent, 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 371 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.21 (1H, singlet, D); 6.95 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 15

2-ethyl-6-hydroxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman

Rf value: 0.42 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 371 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.20 (1H, singlet, D); 6.98 (2H, doublet, J=9 Hz); 8.18 (2H, doublet, J=9 Hz).

PREPARATION 16

6-hydroxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman

Rf value: 0.42 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 399 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.22 (1H, singlet, D); 6.98 (2H, doublet, J=9 Hz); 8.18 (2H, doublet, J=9 Hz).

PREPARATIONS 17-23

Using the corresponding 6-hydroxy compounds prepared as described in Preparations 10–16 above, the procedure of Preparation 4 was repeated, to give the following 6-acetoxy compounds:

PREPARATION 17

6-acetoxy-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)-chroman

Melting at: 132°-134° C.

Rf value: 0.66 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 385 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.31 (3H, singlet); 7.05 (2H, doublet, J=9 Hz); 8.23 (2H, doublet, J=9 Hz).

PREPARATION 18

6-acetoxy-2,7-dimethyl-2-(4-nitrophenoxymethyl)chroman

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 371 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.23 (3H, singlet); 6.95 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 19

6-acetoxy-7-t-butyl-2-methyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Rf value: 0.21 (thin layer chromatography, silica gel, developing solvent: 50:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 427 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.29 (3H, singlet); 6.95 (2H, doublet, J=9 Hz); 8.21 (2H, doublet, J=9 Hz).

PREPARATION 20

6-acetoxy-7,8-dimethoxy-2,5-dimethyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 445 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.33 (3H, singlet); 6.99 (2H, doublet, J=9 Hz); 8.23 (2H, doublet, J=9 Hz).

PREPARATION 21

6-acetoxy-2,5,7,8-tetramethyl-2-[2-(4-nitrophenoxy)ethyl]chroman

Rf value: 0.38 (thin layer chromatography, silica gel, developing solvent: 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 413 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.31 (3H, singlet); 6.95 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 22

6-acetoxy-2-ethyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman

Rf value: 0.44 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of cyclohexane and ethyl acetate).

Mass spectrum (m/e): 413 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.31 (3H, singlet); 6.98 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 23

6-acetoxy-2-isobutyl-5,7,8-trimethyl-2-(4-nitrophenoxymethyl)chroman

Rf value: 0.41 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of cyclohexane and ethyl acetate).

Mass spectrum (m/e): 441 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.32 (3H, singlet); 6.98 (2H, doublet, J=9 Hz); 8.17 (2H, doublet, J=9 Hz).

PREPARATIONS 24–30

Following the procedure described in Preparation 5, but using the appropriate nitrophenoxy compounds prepared as described in Preparations 17–23, the following compounds were prepared:

PREPARATION 24

6-acetoxy-2-(4-aminophenoxymethyl)-5,7,8-trimethylchroman

Melting at 162.5°–164.5° C.

Rf value: 0.11 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 355 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.37 (2H, singlet, D); 6.65 (2H, doublet, J=9 Hz); 6.85 (2H, doublet, J=9 Hz).

PREPARATION 25

6-acetoxy-2-(4-aminophenoxymethyl)-2,7-dimethylchroman

Rf value: 0.52 (thin layer chromatography, silica gel, developing solvent: 1:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 341 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.30 (2H, singlet, D); 6.60 (2H, doublet, J=9 Hz); 6.76 (2H, doublet, J=9 Hz).

PREPARATION 26

6-acetoxy-2-[2-(4-aminophenoxy)ethyl]-7-t-butyl-2-methylchroman

Rf value: 0.15 (thin layer chromatography, silica gel, developing solvent: 5:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 397 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.97–3.53 (2H, broad singlet, D); 6.63 (2H, doublet, J=9 Hz); 6.77 (2H, doublet, J=9 Hz).

PREPARATION 27

6-acetoxy-2-[2-(4-aminophenoxy)ethyl]-7,8-dimethoxy-2,5-dimethylchroman

Rf value: 0.43 (thin layer chromatography, silica gel, developing solvent: 1:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 415 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.23 (2H, broad singlet, D); 6.61 (2H, doublet, J=9 Hz); 6.77 (2H, doublet, J=9 Hz).

PREPARATION 28

6-acetoxy-2-[2-(4-aminophenoxy)ethyl]-2,5,7,8-tetramethylchroman

Rf value: 0.14 (thin layer chromatography, silica gel, developing solvent: 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 383 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.28 (2H, singlet, D); 6.61 (2H, doublet, J=9 Hz); 6.75 (2H, doublet, J=9 Hz).

PREPARATION 29

6-acetoxy-2-(4-aminophenoxymethyl)-2-ethyl-5,7,8-trimethylchroman

Melting at: 123°–124° C.

Rf value: 0.09 (thin layer chromatography, silica gel, developing solvent: 5:1 by volume mixture of cyclohexane and ethyl acetate).

Mass spectrum (m/e): 383 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.8–3.5 (2H, broad singlet, D); 6.59 (2H, doublet, J=9 Hz); 6.76 (2H, doublet, J=9 Hz).

PREPARATION 30

6-acetoxy-2-(4-aminophenoxymethyl)-2-isobutyl-5,7,8-trimethylchroman

Melting at: 137°–138° C.

Rf value: 0.11 (thin layer chromatography, silica gel, developing solvent: 4:1 by volume mixture of cyclohexane and ethyl acetate).

Mass spectrum (m/e): 411 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.7–3.4 (2H, broad singlet, D); 6.61 (2H, doublet, J=9 Hz); 6.77 (2H, doublet, J=9 Hz).

PREPARATIONS 31–38

Following the procedure described in Preparation 6, but using the appropriate starting materials prepared as described in Preparations 24–30 and 41, the following compounds were prepared:

PREPARATION 31

ethyl
3-[4-(6-acetoxy-5,7,8-trimethylchroman-2-yl-methoxy)-phenyl]-2-chloropropionate

Rf value: 0.70 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 474 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.7 (2H, doublet of doublets, J=10 & 5 Hz); 3.13 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.30 (1H, doublet of doublets, J=15 & 7.5 Hz); 4.05–4.46 (6H, multiplet).

PREPARATION 32

ethyl
2-chloro-3-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]phenyl}propionate

Rf value: 0.42 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 460 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.6 (2H, broad triplet, J=6 Hz); 3.11 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.27 (1H, doublet of doublets, J=15 & 7.5 Hz); 4.05–4.5 (6H, multiplet).

PREPARATION 33

ethyl
3-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)-phenyl]-2-chloropropionate

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 460 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.7 (2H, broad triplet, J=6 Hz); 3.12 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.27 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.8–4.45 (5H, multiplet).

PREPARATION 34

ethyl
3-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]phenyl}-2-chloropropionate

Rf value: 0.53 (thin layer chromatography, silica gel, developing solvent: 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 516 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.7 (2H, broad triplet, J=6 Hz); 3.11 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.27 (1H, doublet of doublets, J=15 & 7.5 Hz); 4.03–4.50 (5H, multiplet).

PREPARATION 35

ethyl
3-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]phenyl}-2-chloropropionate

Rf value: 0.45 (thin layer chromatography, silica gel, developing solvent: 9:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 534 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.6 (2H, broad triplet, J=6 Hz); 3.10 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.27 (1H, doublet of doublets, J=15 & 7.5 Hz); 4.07–4.46 (5H, multiplet).

PREPARATION 36

ethyl
3-{4-[2-(6-acetoxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]phenyl}-2-chloropropionate

Rf value: 0.39 (thin layer chromatography, silica gel, developing solvent: 20:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 502 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.6 (2H, broad triplet, J=6 Hz); 3.06 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.32 (1H, doublet of doublets, J=15 & 7.5 Hz); 4.05–4.45 (5H, multiplet).

PREPARATION 37

ethyl
3-[4-(6-acetoxy-2-ethyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate

Rf value: 0.33 (thin layer chromatography, silica gel, developing solvent: 100:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 502 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.6 (2H, broad triplet, J=6 Hz); 3.05 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.30 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.90–4.45 (5H, multiplet).

PREPARATION 38

ethyl
3-[4-(6-acetoxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate

Rf value: 0.44 (thin layer chromatography, silica gel, developing solvent: 100:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 530 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.6 (2H, broad triplet, J=7 Hz); 3.05 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.30 (1H, doublet of doublets, J=15 & 7.5 Hz); 3.90–4.45 (5H, multiplet).

PREPARATION 39

2-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)ethanol

Following the procedure described in Preparation 1, 2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethanol was reacted with benzyl bromide and treated and purified to give the title compound.

Rf value: 0.31 (thin layer chromatography, silica gel, developing solvent: 10:1 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 340 (M^+).

Nuclear Magnetic Resonance Spectrum ($CDCl_3+D_2O$) δ ppm: 1.31 (3H, singlet); 1.67–2.37 (4H, multiplet); 2.10 (3H, singlet); 2.17 (3H, singlet); 2.23 (3H, singlet); 2.65 (2H, broad triplet, J=6 Hz); 3.90 (2H, triplet, J=6 Hz); 4.72 (2H, singlet); 7.3–7.65 (5H, multiplet).

PREPARATION 40

6-Benzyloxy-2,5,7,8-tetramethyl-2-[2-(4-nitrophenoxy)ethyl]chroman

2-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)ethanol (prepared as described in Preparation 39) was reacted with p-chloronitrobenzene and the reaction mixture was treated and purified as described in Preparation 2, to give the title compound.

Rf value: 0.43 (thin layer chromatography, silica gel, developing solvent: benzene).

Mass spectrum (m/e): 461 (M^-).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.37 (3H, singlet); 1.90 (2H, triplet, J=6 Hz); 2.11 (3H, singlet); 2.18 (3H, singlet); 2.24 (3H, singlet); 2.0–2.3 (2H, nd); 2.66 (2H, triplet, J=6 Hz); 4.32 (2H, triplet, J=6 Hz); 4.73 (2H, singlet); 6.94 (2H, doublet, J=9 Hz); 7.3–7.65 (5H, multiplet); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 41

2-[2-(4-Aminophenoxy)ethyl]-6-hydroxy-2,5,7,8-tetramethylchroman

6-Benzyloxy-2,5,7,8-tetramethyl-2-[2-(4-nitrophenoxy)ethyl]chroman (prepared as described in Preparation 40) was catalytically reduced and then the reaction mixture was processed as described in Preparation 5. The resulting crude product was purified by silica gel column chromatography and the title compound was obtained from the fractions eluted with a 4:1 by volume mixture of benzene and ethyl acetate.

Rf value: 0.36 (thin layer chromatography, silica gel, developing solvent: 3:2 by volume mixture of benzene and ethyl acetate).

Mass spectrum (m/e): 341 (M^-).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.32 (3H, singlet); 1.87 (2H, triplet, J=6 Hz); 2.10 (6H, singlet); 2.15 (3H, singlet); 2.0–2.3 (nd); 2.64 (2H, broad triplet, J=6 Hz); 3.2–4.1 (2H, broad singlet); 4.12 (3H, triplet, J=6 Hz); 6.60 (2H, doublet, J=9 Hz); 6.75 (2H, doublet, J=9 Hz).

PREPARATION 42

6-Hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 3.9 g of 2,5-dihydroxy-3,4,6-trimethylacetophenone, 3.9 g of 4-nitrophenoxyacetone, 2.0 g of pyrrolidine and 15 g of toluene was left standing at room temperature for 2 days. Dilute hydrochloric acid was then added to the reaction mixture and the mixture was extracted with diethyl ether. The remaining aqueous layer was again extracted with ethyl acetate and the ethyl acetate extract was added to the ethereal extract. The resulting mixture was dried over anhydrous sodium sulfate. The solvent was distilled off from the mixture. Hexane was added to the resulting residue, and the crystals thus precipitated were collected by filtration. The crystals were subjected to silica gel column chromatography, eluted with a 5:1 by volume mixture of hexane and ethyl acetate, and then recrystallized from ethyl acetate, to yield 6-hydroxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one. Its melting point was 199°–204° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide) δ ppm: 1.43 (3H, singlet); 2.01 (3H, singlet); 2.14 (3H, singlet); 2.46 (3H, singlet); 2.67 (1H, doublet, J=16 Hz); 3.03 (1H, doublet, J=16 Hz); 4.31 (2H, singlet); 7.19 (2H, doublet, J=9 Hz); 7.92 (1H, singlet); 8.21 (2H, doublet, J=9 Hz).

PREPARATION 43

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 17.7 g of 5-acetoxy-2-hydroxy-3,4,6-trimethylacetophenone, 14.6 g of 4-nitrophenoxyacetone, 7.5 g of pyrrolidine and 60 ml of benzene was left standing at room temperature for one day, and then the mixture was refluxed for 7 hours using a water separator. At the end of this time, water and ethyl acetate were added to the reaction mixture and the organic layer was separated. It was then dried over anhydrous sodium sulfate. The solvent was distilled off and the resulting residue was subjected to silica gel column chromatography, eluted with a 2:1 by volume mixture of hexane and ethyl acetate, to yield 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one.

Rf value: 0.17 (thin layer chromatography, silica gel, developing solvent: hexane:ethyl acetate=3:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.56 (3H, singlet); 2.10 (6H, singlet); 2.36 (3H, singlet); 2.43 (3H, singlet); 2.70 (1H, doublet, J=15 Hz); 3.06 (1H, doublet, J=15 Hz); 4.11 (1H, doublet, J=10 Hz); 4.24 (1H, doublet, J=10 Hz); 6.98 (2H, doublet, J=9 Hz); 8.20 (2H, doublet, J=9 Hz).

PREPARATION 44

6-Acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman-4-one

Hydrogen gas was passed for 2 hours through a mixture of 3.6 g of 6-acetoxy-2,5,7,8-tetramethyl-2-(4-nitrophenoxymethyl)chroman-4-one, 1 g of 10% w/w palladium-on-carbon and 100 ml of methanol at room temperature under atmospheric pressure. The catalyst was then removed by filtration and the filtrate was condensed by evaporation under reduced pressure. The residue was subjected to silica gel column chromatography, eluted with a 2:1 by volume mixture of hexane and ethyl acetate, and the resulting crude product was recrystallized from acetone, to yield 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman-4-one. Its melting point was 177°–178° C.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.49 (3H, singlet); 2.09 (3H, singlet); 2.12 (3H, singlet); 2.33 (3H, singlet); 2.42 (3H, singlet); 2.65 (1H, doublet, J=15 Hz); 3.07 (1H, doublet, J=15 Hz); 3.2–3.6 (2H, broad singlet); 3.91 (1H, doublet, J=10 Hz); 4.06 (1H, doublet, J=10 Hz); 6.60 (2H, doublet, J=9 Hz); 6.75 (2H, doublet, J=9 Hz).

PREPARATION 45

Ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate

3 ml of concentrated hydrochloric acid and then an aqueous solution of 700 mg of sodium nitrite in 1.1 ml of water were added dropwise to a mixture of 2.1 g of 6-acetoxy-2-(4-aminophenoxymethyl)-2,5,7,8-tetramethylchroman-4-one and 26 ml of acetone, whilst cooling with ice. The mixture was stirred for 30 minutes at the same temperature. 7 g of ethyl acrylate were then added, after which cuprous oxide was added gradually, while keeping the reaction temperature at 30°–35° C. The reaction mixture was then stirred for 1 hour at room temperature. Water and benzene were added to the reaction mixture. The benzene layer was separated, washed with water and dried over anhydrous sodium sulfate. Benzene was distilled off and the residue was subjected to silica gel column chromatography, eluted with a 3:1 by volume mixture of hexane and ethyl acetate, to yield ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate.

Rf value: 0.21 (thin layer chromatography, silica gel, developing solvent: hexane:ethyl acetate = 3:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.24 (3H, triplet, J = 7 Hz); 1.51 (3H, singlet); 2.10 (3H, singlet); 2.12 (3H, singlet); 2.34 (3H, singlet); 2.43 (3H, singlet); 2.67 (1H, doublet, J = 15 Hz); 3.07 (1H, doublet of doublets, J = 7.5 & 15 Hz); 3.10 (1H, doublet, J = 15 Hz); 3.32 (1H, doublet of doublets, J = 7.5 & 15 Hz); 4.06 (2H, singlet); 4.18 (2H, quartet, J = 7 Hz); 3.9–4.5 (1H, nd); 6.84 (2H, doublet, J = 9 Hz); 7.15 (2H, doublet, J = 9 Hz).

PREPARATION 46

7-t-Butyl-6-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one

In a similar manner to Preparation 42, a mixture of 2.0 g of 4-t-butyl-2,5-dihydroxyacetophenone, 1.9 g of 4-nitrophenoxyacetone, 1.0 g of pyrrolidine and 10 ml of benzene was allowed to stand at room temperature for 2 days. To the reaction mixture was then added 10% w/w hydrochloric acid, and the crude product was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, and the residue obtained by removing the solvent was subjected to silica gel column chromatography, eluted with a 10:1 by volume mixture of benzene and ethyl acetate. The resulting crude crystals were washed with cyclohexane to give the desired 7-t-butyl-6-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one.

Melting point: 205°–209° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.39 (3H, singlet); 1.53 (9H, singlet); 2.70 (1H, doublet, J = 16.5 Hz); 3.05 (1H, doublet, J = 16.5 Hz); 4.37 (2H, singlet); 6.80 (1H, singlet); 7.18 (2H, doublet, J = 10 Hz); 7.22 (1H, singlet); 8.22 (2H, doublet, J = 10 Hz); 8.31 (1H, singlet, D).

PREPARATION 47

6-Acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one

A mixture of 1.7 g of 7-t-butyl-6-hydroxy-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one, 1 ml of acetic anhydride and 10 ml of pyridine was allowed to stand at room temperature for 1 day. The reaction mixture was then poured into ice-water and stirred for 2 hours, and the crude substance was extracted with benzene. The organic solution was washed successively with 3N hydrochloric acid, water, a saturated aqueous solution of sodium bicarbonate and water, and dried over anhydrous sodium sulfate. The solvent was evaporated off under reduced pressure, and the crude product thus obtained was recrystallized from a 10:1 by volume mixture of benzene and ethyl acetate, to give the desired 6-acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)chroman-4-one.

Melting point: 82°–84° C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated acetone) δ ppm: 1.33 (9H, singlet); 1.57 (3H, singlet); 2.33 (3H, singlet); 2.82 (1H, doublet, J = 16.5 Hz); 3.13 (1H, doublet, J = 16.5 Hz); 4.42 (2H, singlet); 6.93 (1H, singlet); 7.25 (2H, doublet, J = 9 Hz); 7.44 (1H, singlet); 8.22 (2H, doublet, J = 9 Hz).

PREPARATION 48

6-Acetoxy-2-(4-aminophenoxymethyl)-7-t-butyl-2-methylchroman-4-one

In a similar manner to Preparation 44, 0.9 g of 6-acetoxy-7-t-butyl-2-methyl-2-(4-nitrophenoxymethyl)-chroman-4-one was dissolved in 20 ml of acetic acid, and catalytic hydrogenation was performed for 5.5 hours with a hydrogen pressure of 45–55 lb/sq. inch (3.1–3.8 bars), using Pearl's apparatus, in the presence of 0.4 g of 10% w/w palladium-on-carbon. The palladium-on-carbon was removed by filtration from the reaction mixture and washed with acetic acid. The filtrate and the washings were combined, and the mixture was poured into ice-water, neutralized with sodium carbonate, and extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was subjected to silica gel column chromatography, eluted with a 5:1 by volume mixture of benzene and ethyl acetate, to give the desired 6-acetoxy-2-(4-aminophenoxymethyl)-7-t-butyl-2-methylchroman-4-one.

Rf value: 0.24 (thin layer chromatography, silica gel, developing solvent: benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.35 (9H, singlet); 1.52 (3H, singlet); 2.30 (3H, singlet); 2.67 (1H, doublet, J = 16.5 Hz); 3.07 (1H, doublet, J = 16.5 Hz); 3.20–3.60 (2H, broad, D); 3.92 (1H, doublet, J = 10.5 Hz); 4.07 (1H, doublet, J = 10.5 Hz); 6.58 (2H, doublet, J = 10 Hz); 6.75 (2H, doublet, J = 10 Hz); 6.98 (1H, singlet); 7.49 (1H, singlet).

PREPARATION 49

Ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)phenyl]-2-chloropropionate

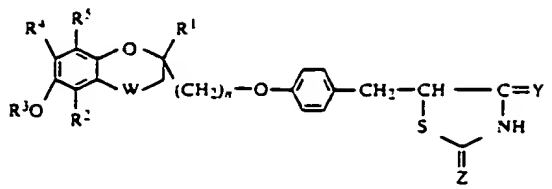
In a similar manner to Preparation 45, to a mixture of 0.42 g of 6-acetoxy-2-(4-aminophenoxymethyl)-7-t-butyl-2-methylchroman-4-one and 5 ml of acetone were added dropwise, whilst cooling with ice, 0.2 ml of concentrated hydrochloric acid and then a solution of 0.09 g of sodium nitrite in 0.5 ml of water. 1.1 g of ethyl acrylate were then added dropwise, after which 16 mg of cuprous oxide were added gradually to the mixture, whilst keeping its temperature at 40°–43° C. Evolution of nitrogen ceased after about 30 minutes. Benzene was added to the reaction mixture, and the organic layer was separated. The resulting benzene extract was washed with water and dried over anhydrous sodium sulfate. The residue after evaporation of the benzene was subjected to silica gel column chromatography, eluted with a 20:1 by volume mixture of benzene and ethyl acetate, to give the desired ethyl 3-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)-phenyl]-2-chloropropionate.

Rf value: 0.61 (thin layer chromatography, silica gel, developing solvent: benzene:ethyl acetate = 5:1 by volume).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.25 (3H, triplet, J = 7 Hz); 1.35 (9H, singlet); 1.55 (3H, singlet); 2.32 (3H, singlet); 2.70 (1H, doublet, J = 16.5 Hz); 2.95–3.50 (3H, multiplet); 3.90–4.50 (5H, multiplet); 6.87 (2H, doublet, J = 9 Hz); 7.00 (1H, singlet); 7.17 (2H, doublet, J = 9 Hz); 7.50 (1H, singlet).

We claim:

1. Compounds of formula (I):



in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2-$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

2. Compounds as claimed in claim 1, in which: R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or one of said heterocyclic acyl groups.

3. Compounds as claimed in claim 1, in which: Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1 or C_2 alkoxy group.

4. Compounds as claimed in claim 3, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or $>CO$ group.

5. Compounds as claimed in claim 4, in which R^3 represents a hydrogen atom, a C_1–C_5 aliphatic acyl group, or the benzoyl or nicotinoyl group.

6. Compounds as claimed in claim 5, in which: R^1 and R^4 are the same or different and each represents a C_1–C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

7. Compounds as claimed in claim 1, in which: W represents the $-CH_2-$ or $>CO$ group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1–C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

8. Compounds as claimed in claim 7, in which n is 1.

9. Compounds as claimed in claim 7 or claim 8, in which W represents the $-CH_2-$ group.

10. Compounds as claimed in claim 1, selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

5-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

and pharmaceutically acceptable salts thereof.

11. The compound as claimed in claim 1.

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

12. The compound as claimed in claim 1.

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

13. The compound as claimed in claim 1, 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione and pharmaceutically salts thereof.

14. The compound as claimed in claim 1, 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

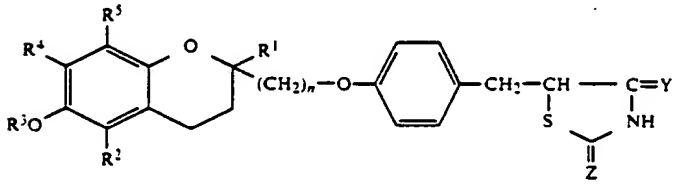
15. The compound as claimed in claim 1, 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

16. The compound as claimed in claim 1, 5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

17. The compound as claimed in claim 1, 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

18. The compound as claimed in claim 1, 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.

19. Compounds of formula (Ia):



(Ia)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

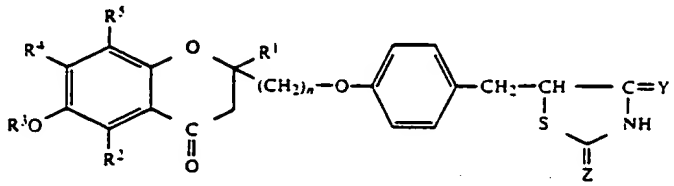
R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

20. Compounds of formula (Ib):



(Ib)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

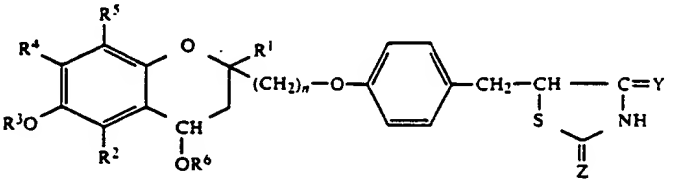
R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

21. Compounds of formula (Ic):



(Ic)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy,

halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

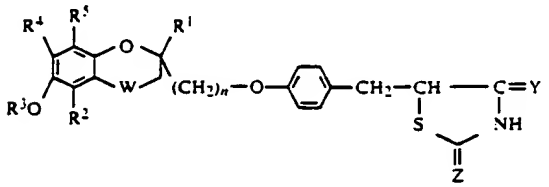
R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

22. Compounds as claimed in claim 1 or claim 19, which are salts with cations.

23. Compounds as claimed in claim 1 or claim 19, in the form of the sodium salt.

24. A pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one active compound in admixture with a pharmaceutically acceptable carrier or diluent, wherein said active compound is selected from compounds of formula (I):



(I)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2-$, $>CO$ or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

25. Compositions as claimed in claim 24, in which: R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or one of said heterocyclic acyl groups.

26. Compositions as claimed in claim 24, in which: Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; R^3 represents hydrogen, a C_1–C_6 aliphatic acyl group, one of said aromatic acyl groups or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1 or C_2 alkoxy group.

27. Compositions as claimed in claim 26, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or $>CO$ group.

28. Compositions as claimed in claim 27, in which R^3 represents a hydrogen atom, a C_1–C_5 aliphatic acyl group, or the benzoyl or nicotinoyl group.

29. Compositions as claimed in claim 28, in which: R^1 and R^4 are the same or different and each represents a C_1–C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

30. Compositions as claimed in claim 24, in which: W represents the $-CH_2-$ or $>CO$ group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1–C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents hydrogen or a C_1–C_4 aliphatic acyl group.

31. Compositions as claimed in claim 30, in which n is 1.

32. Compositions as claimed in claim 30 or claim 17, in which W represents the $-CH_2-$ group.

33. Compositions as claimed in claim 24, wherein said active compound is selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one
5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one
5-{4-[2-(6-actoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

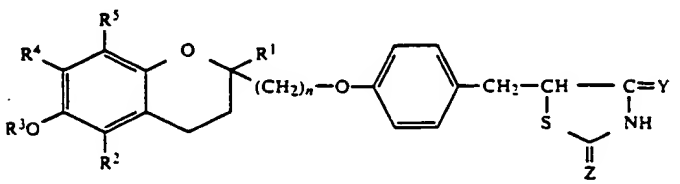
and pharmaceutically acceptable salts thereof.

34. Compositions as claimed in claim **24**, wherein said active compound is selected from the group consisting of:

5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione
5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione
5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

and pharmaceutically acceptable salts thereof.

35. Compositions as claimed in claim **24**, in which said active compound is selected from compounds of formula (Ia):



(Ia)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

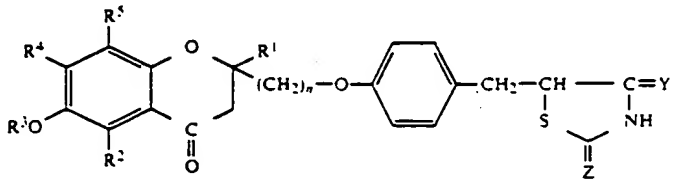
R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

36. Compositions as claimed in claim **24**, in which said active compound is selected from compounds of formula (Ib):



(Ib)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represent hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

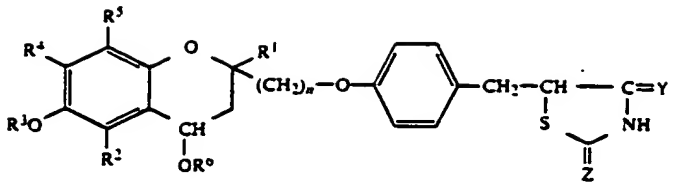
n is 1, 2 or 3;

and

Y and Z are the same or different and each represents the oxygen atom or the amino group;

and pharmaceutically acceptable salts thereof.

37. Compositions as claimed in claim **24**, in which said active compound is selected from compounds of formula (Ic):



(Ic)

in which:

R^1 and R^2 are the same or different and each represents hydrogen or a C_1–C_5 alkyl group;

R^3 represents hydrogen; C_1–C_6 aliphatic acyl; (C_5–C_7 cycloalkane)carbonyl; benzoyl, benzoyl substituted with one to three substituents selected from the group of C_1–C_4 alkyl, C_1–C_4 alkoxy, hydroxy, halogen, nitro, amino and di(C_1–C_4 alkyl)amino; naphthoyl; 4–7 membered heterocyclic acyl wherein heterocyclic moiety has O, S or N hetero atoms; phenyl(C_2–C_3)aliphatic acyl; cinnamoyl; (C_1–C_6 alkoxy)carbonyl; or benzoyloxycarbonyl;

R^4 and R^5 are the same or different and each represents hydrogen, a C_1–C_5 alkyl group or a C_1–C_5 alkoxy group, or R^4 and R^5 together represent a C_1–C_4 alkylenedioxy group;

n is 1, 2 or 3;

R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3; and

Y and Z are the same or different and each represents the oxygen atom or the imino group; and pharmaceutically acceptable salts thereof.

38. Compositions as claimed in claim 24 or claim 35, wherein said active compound is in the form of a salt with a cation.

39. Compositions as claimed in claim 24 or claim 35, wherein said active compound is in the form of the sodium salt.

* * * * *

EXHIBIT 5

EXHIBIT 5

CERTIFICATE OF CORRECTION

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,572,912 PAGE 1 OF 2.

DATED : February 25, 1986

INVENTOR(S) : Takao YOSHIOKA et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the title page of the patent:

Under the heading of "References Cited", change the name of the inventor of the second listed reference to --Kawamatsu--.

Insert a third reference as follows:

--4,287,200 9/1981 Kawamatsu--.

In the Abstract:

The left-hand column, line 8, change "$C_1$14C_4" to --C_1-C_4--.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,572,912

DATED : February 25, 1986

INVENTOR(S) : Takao YOSHIOKA et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 19, equation (Ie), appearing at lines 10 - 15, change the "W" in the second segment of equation to

$$-- \underset{\underset{OR^{61}}{|}}{CH} --.$$

Column 62 (Claim 32), line 27, change "claim 30 or claim 17" to --claim 30 or claim 31--.

Signed and Sealed this

Twentieth Day of January, 1987

Attest:

Priscilla H. Fuller

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

EXHIBIT 6

EXHIBIT 6

MAINTENANCE FEE PAYMENT RECEIPTS

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001933

RECEIVED

APR 28 1989

FRISHAUF, HOLTZ, GOODMAN & WOODWARD, P.C.

FRISHAUF, HOLTZ, GOODMAN &
WOODWARD, P.C.
600 THIRD AVENUE - 30TH FLOOR
NEW YORK, NY 10016

DATE MAILED
04/25/89

069714

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,547,513	173	450	----	06/679,466	10/15/85	12/07/84	04	NO	PAID
2	4,550,143	173	450	----	06/616,601	10/29/85	06/01/84	04	NO	PAID
3	4,550,145	173	450	----	06/559,381	10/29/85	12/08/83	04	NO	PAID
4	4,550,134	173	450	----	06/644,784	10/29/85	08/27/84	04	NO	PAID
5	4,572,912	173	450	----	06/644,996	02/25/86	08/28/84	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	84874
2	84364
3	
4	84565
5	84566

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTOL 477-03 v. 1.88)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
001933

FRISHAUF, HOLTZ, GOODMAN &
WOODWARD, P.C.
600 THIRD AVENUE - 30TH FLOOR
NEW YORK, NY 10016

9200

DATE MAILED
03/22/93

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,572,912	184	1870	----	06/644,996	02/25/86	08/28/84	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	84566-M6

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

EXHIBIT 7

EXHIBIT 7

IND SUBMISSION LETTER

Oxford Research International Corp.

1425 BROAD STREET CLIFTON, NEW JERSEY 07013-4221
(201) 777-2800

January 30, 1989
Ref. No. 19-91

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine Drug Products

Dear Dr. Sobel:

Submitted herewith in triplicate is an initial IND application provided on behalf of Sankyo Company Ltd., Tokyo, Japan. This IND contains information on Sankyo research compound CS-045, an oral hypoglycemic agent.

Also provided with this letter, is a letter dated January 4, 1989 from Dr. Akira Ogiso, Director, Research Planning Department of Sankyo Company, Ltd. authorizing Oxford Research International Corp. as the agent and representative to the FDA on behalf of Sankyo Company Ltd. for this IND.

Provided within this IND is a clinical protocol entitled, "Mechanism of Action Studies on CS-045, A New Oral Hypoglycemic Agent in Patients with Non-Insulin Dependent Diabetes Mellitus". This study will be conducted by Dr. Jerrold M. Olefsky, University of California, San Diego School of Medicine.

Please do not hesitate to contact me if you have any questions concerning the IND.

Thank you for your cooperation.

Sincerely,

William M. Troetel, Ph.D.
Senior Vice President

Enclosure

WEST COAST OFFICE
(213) 670-5300

MIDWEST OFFICE
(515) 472-1833

TELEX: 170942 OXFRD
FAX: (201) 777-9847

SANKYO CO., LTD.

Cable: "DIASTASE TOKYO" Telex: "724838 DIASTASE"
Tel: (03) 562-0411 Fax: (03) 561-5409
No. 7-12, Ginza 2-chome, Chuo-ku,
Tokyo 104, Japan.

January 4, 1989

Department of Health and Human Services
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857, USA

Attention: Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine Drug Products

Dear Dr. Sobel:

This letter will serve to inform you that Dr. William M. Troetel, Senior Vice President, Oxford Research International Corp., 1425 Broad Street, Clifton, New Jersey 07013, USA, has been named our agent and representative in the United States for filing of an Investigational New Drug Application for CS-045, a novel oral hypoglycemic, and subsequent clinical studies.

This letter authorizes Dr. Troetel and Oxford Research to act on behalf of Sankyo Company, Ltd. to submit filings to FDA and to receive responses from FDA on our behalf. They may also from time to time, request meetings with various divisions within FDA to discuss matters pertinent to research interests of the Sankyo Company, Ltd.

Please feel free to contact me if there are any questions concerning this matter.

Thank you for your cooperation.

Sincerely,

Akira Ogiso, Ph.D.
Director
Research Planning Department

cc: William M. Troetel, Ph.D.
Oxford Research International Corp.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Sankyo Co., Ltd.

2. DATE OF SUBMISSION
January 30, 1989

3. ADDRESS *(Number, Street, City, State and Zip Code)*
7-12, 2-Chome, Ginza
Chuo-ku
Tokyo 104, Japan

4. TELEPHONE NUMBER *(Include Area Code)*
011-813-562-0411

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
CS-045

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Oral hypoglycemic agent

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☒ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

---

10. SERIAL NUMBER: 000

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (8/87) PREVIOUS EDITION IS OBSOLETE.

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- [X] 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- [X] 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- [X] 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- [X] 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - [X] b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- [X] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - [X] a. Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- [X] 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- [X] 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- [ ] 10. Additional information *[21 CFR 312.23 (a) (10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [X] YES [ ] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [X] YES [ ] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Stanley B. Garbus, M.D.
Oxford Research International Corp.
1425 Broad Street
Clifton, N.J. 07013 Tel: 201 777-2800

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Akira Ogiso, Ph.D.; Director, Research Planning Department
Hiroyoshi Horikoshi, D.V.M., Ph.D., Chief Researcher, Biological Research Labs. Sankyo Co., Ltd. Tokyo, Japan

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND or on earlier notification by FDA. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
William M. Troetel, Ph.D. Senior Vice President	William M. Troetel	
18. ADDRESS *(Number, Street, City, State and Zip Code)* Oxford Research International Corp 1425 Broad Street Clifton, N.J. 07013	19. TELEPHONE NUMBER *(Include Area Code)* Tel:201-777-2800 Fax:201-777-9847	20. DATE

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec. 1001.)

•U.S.GPO:1987-O-181-338/64852

EXHIBIT 8

EXHIBIT 8

IND ACKNOWLEDGEMENT LETTER

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 32,703

FEB -9 1989

Sankyo Co., Ltd.
Attention: William M. Troetel, Ph.D.
7-12, 2-Chome, Ginza
Chuo-ku
Tokyo 104, Japan

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND number assigned: 32,703

Sponsor: Sankyo Co., Ltd.

Name of Drug: CS-045

Date of Submission: January 30, 1989

Date of Receipt: February 7, 1989

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming adverse reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

32,703

s sponsor of the clinical study proposed under this IND, you are now free to btain supplies of the investigational drug.

lease forward all future communications concerning this IND in TRIPLICATE, DENTIFIED WITH THIS IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research, HFD-510
Attention: DOCUMENT CONTROL ROOM 14B03
5600 Fishers Lane
Rockville, Maryland 20857

:hould you have any questions concerning this IND, please call me at 301) 443- 3510

Sincerely yours,

JEAN M WEBER

Consumer Safety Officer
Division of Metabolism and Endocrine
Drug Products
Center for Drug Evaluation and Research

EXHIBIT 9

EXHIBIT 9

OCTOBER 12, 1990 IND TRANSFER LETTER

PHI 763-3172 FAX.: (212) 308-2491

SANKYO U.S.A. CORPORATION

780 THIRD AVENUE, SUITE 2301
NEW YORK, N.Y. 10017

October 12, 1990

Solomon Sobel, M.D.
Director, Division of Metabolic
and Endocrine Drug Products/HFD-510
Attn: Document Control Room 14B-03
Office of Drug Research and Review II
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857 USA

Re: IND 32,703
CS-045 Tablets
Serial/Amendment #008

Dear Dr. Sobel:

This is to advise you that effective October 12, 1990, Sankyo U.S.A. Corporation will be the sponsor for the Investigational New Drug Application, IND #32,703, relating to the oral hypoglycemic agent, CS-045 Tablets. This IND is being transferred from Sankyo Co. Ltd., Tokyo, as stated in the enclosed letter addressed to you, dated October 5, 1990, from Sankyo Co. Ltd. Tokyo, as well as in the letter, dated October 9, 1990, from Oxford Research International Corporation.

Sankyo U.S.A. Corporation accepts the responsibility for this IND and agrees to comply with all applicable FDA regulations. Enclosed is a completed and signed Form 1571.

In this regard, we are also enclosing the curriculum vitae of the staff of Sankyo U.S.A. Corporation who will be responsible for monitoring the conduct and progress of further CS-045 clinical investigations as well as for the review and evaluation of information relevant to the safety of this compound.

We also acknowledge that a request was made by you, in a letter dated May 19, 1989, for additional data prior to the initiation of further studies. We will now compile data towards satisfying this request, but we believe that a meeting would be helpful to clarify some of the issues.

After compiling data, we will submit these to you and formulate questions we wish to pursue; at that time, we will request a date for a meeting.

Thank you for your kind assistance in this matter.

Sincerely,

Paul G. Gooding.

Paul G. Gooding, M.B., B.S.
Director, Clinical Research
for Sankyo U.S.A. Corporation

PGG/ye

Submitted in triplicate.

Enclosures: Letter, Sankyo Co. Ltd. (Tokyo) to FDA dated October 5, 1990
Letter, Sankyo U.S.A. Corporation to FDA dated October 12, 1990
1571 Form (Original and 2 copies)
Letter, Oxford Research International Corporation to FDA dated October 9, 1990

EXHIBIT 10A

EXHIBIT 10A

APRIL 26, 1991 IND TRANSFER LETTER

PHONE: (212) 753-3172

FAX.: (212) 308-2491

SANKYO U.S.A. CORPORATION

780 THIRD AVENUE, SUITE 2301
NEW YORK, N.Y. 10017

April 26, 1991

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine
Drug Products/HFD-510
Attn: Document Control Room 14B-03
Office of Drug Research and Review II
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857, USA

Re: IND #32,703
CS-045 Tablets
Amendment 012

Dear Dr. Sobel:

This is to advise you that effective April 26, 1991, Sankyo U.S.A. Corporation will transfer the Investigational New Drug Application, IND #32,703, relating to the oral hypoglycemic agent CS-045 Tablets, and all amendments thereto except:

(1) Section 7(a), Chemistry, Manufacturing and Controls (Drug Substance), Vol. 1, pages 214 to and including 407 of the original application

(2) Stability of CS-045 (Drug Substance) included in the 1990 Annual Report, Section III, pages 6-19 inclusive, submitted to the FDA on April 16, 1990 (IND #32,703, Amendment 006)

(3) items/comments 1 and 2 of the Chemistry, Manufacturing and Controls (Drug Substance) section contained in our November 20, 1990 submission to the FDA (IND #32,703, Amendment 009)

to: Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48106-1047

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, as the new sponsor, will confirm acceptance of responsibility for this IND and will formally agree to comply with all applicable F.D.A. Regulations, via letter, in the immediate future.

Please address all future communications relating to this IND to Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, at the address noted above, for the attention of:

Irwin G. Martin, Ph.D.
Director, Worldwide Regulatory Affairs
Tel: (313) 996-7756
FAX: (313) 996-7890

IND #32,703 was initially submitted to the F.D.A. on January 30, 1989, by Oxford Research International Corporation, acting as agent and representative to the F.D.A. on behalf of Sankyo Co., Ltd., Tokyo, Japan. Subsequently, on October 12, 1990, IND #32,703 was formally transferred to Sankyo U.S.A. Corporation, New York, N.Y. (Amendment 008).

Parke-Davis Pharmaceutical Division, Warner-Lambert Company has been made aware that:

1. A request was made from HFD-510, in a letter dated May 19, 1989, for additional data prior to the initiation of further studies.

2. A partial answer to the questions raised was submitted on November 20, 1990 (Amendment 009), however, certain clinical pharmacokinetic concerns were not addressed in this submission.

Sankyo Co. Ltd., Tokyo, Japan has separately filed a Type I Drug Master File (DMF #9047) and a Type II Drug Master File (DMF #9048) relating to the Chemistry and Manufacturing Controls section for the new drug substance, and has provided authorization for Parke-Davis Pharmaceutical Division, Warner-Lambert Company, to incorporate the information contained in these D.M.F.'s into their IND by cross reference.

Please add this information to the subject file.

Thank you for your kind assistance in this matter.

Sincerely,

Paul G. Gooding.

Paul G. Gooding, M.B., B.S.
Vice President, Medical
for Sankyo U.S.A. Corporation

PGG/ye

Submitted in triplicate

cc: Dr. Irwin G. Martin, Ph.D.
Director, Worldwide Regulatory Affairs
Parke-Davis, Warner Lambert

EXHIBIT 10B

EXHIBIT 10B

MAY 13, 1991 IND TRANSFER LETTER

PARKE-DAVIS
Pharmaceutical Research Division
Warner-Lambert Company

May 13, 1991

IND 32,703
Serial No. 013
CS-045 (CI-991)

Re: Transference of IND

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine Drug
Products (HFD-510)
Document Control Room 14B-03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Please be advised that effective immediately, sponsorship of IND 32,703 is transferred from Sankyo U.S.A. Corporation to Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company. A copy of the transfer letter from Sankyo is attached.

Parke-Davis assumes full responsibility for all matters relating to this IND except for drug substance manufacturing. We have received a complete copy of the IND from Sankyo Company, Ltd except for drug substance manufacturing information. Sankyo U.S.A. Corporation has opened a Type I Drug Master File (DMF #9047) and a Type II Drug Master File (DMF #9048) for drug substance updates and communication. Parke-Davis hereby commits to amending this IND with notification of any changes or updates to the drug substance information relevant to this IND as contained in the Sankyo DMFs #9047 and #9048. All communications concerning the drug substance should, therefore, be directed to Sankyo U.S.A. Corporation via DMFs #9047 and #9048.

CS-045 is also known by the Parke-Davis code name of CI-991. Future correspondence to IND 32,703 will refer to CI-991 exclusively.

Enclosed is a summary of the training and experience of the Parke-Davis medical monitor, Rebecca Norris, M.D.

Only one clinical study has been conducted under IND 32,703. Dr. Jerrold Olefsky has been notified of the change in the IND sponsors. His clinical study report is being finalized and will be submitted to the IND by Parke-Davis when it is completed.

We commit to amend the IND within 60 days to cover any changes resulting from new ownership, and to provide for subsequent changes by amendment in accord with IND regulations.

Please address all communications concerning this IND to the undersigned.

Sincerely,

Irwin G. Martin, Ph.D.
Senior Director
Worldwide Regulatory Affairs

Telephone 313\996-7756
Fax 313\996-7890

IGM/rt43091

Attachment

EXHIBIT 11A

EXHIBIT 11A

NDA SUBMISSION LETTER FOR PRELAY™

PHONE: (212) 753-3172

FAX.: (212) 308-2491

SANKYO U.S.A. CORPORATION

780 THIRD AVENUE, SUITE 1700
NEW YORK, N.Y. 10017

July 31, 1996

NDA 20-719
Ref. No. 1
Vol 1.1
Prelay™ (troglitazone) Tablets

Re: Original New Drug Application
User Fee I.D. No. 3008

Food and Drug Administration
Document and Records Section
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir/Madam:

Pursuant to § 505(b)(1) of the FDC Act, enclosed is a new drug application (20-719) for Prelay™ (troglitazone) Tablets. This NDA provides evidence for the use of troglitazone as an adjunct to diet in the treatment of Type II diabetes in patients who are inadequately controlled by insulin therapy.

The NDA number 20-719 was preassigned to this application on March 20, 1996.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1996 application fee ($102,000.00) has been sent to the Food and Drug Administration in care of Mellon Bank, Philadelphia, Pennsylvania on July 10, 1996. A User Fee Cover Sheet, Form FDA 3397, follows this cover letter.

The primary data in support of this NDA were developed by Sankyo U.S.A. Corporation and the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company under IND 32,703. Other data were generated by Sankyo Co., Ltd., Japan and GlaxoWellcome Ltd., U.K.

Please include by cross-reference the complete contents of NDA 20-720 for Rezulin™ (troglitazone) Tablets, which is submitted by Parke-Davis concurrently with this NDA. Permission to cross reference the Parke-Davis NDA has been granted to Sankyo U.S.A. Corporation, and a copy of the Parke-Davis letter providing this permission is attached to this letter. Please also include in this NDA by cross reference the presubmission and any subsequent amendments to NDA 20-720. Sankyo U.S.A. Corporation has been provided with a complete copy of NDA 20-720.

As noted on the attached 356h, only Item 4.c.i., Labels and Labeling, and Item 13, Patent Information and Request for Exclusivity, are provided herein. The content of the labels and labeling are identical to that of Rezulin except that the brand name has been changed to Prelay and the NDC numbers will differ.

Reference to all Drug Master Files made in NDA 20-720 are also made herein. Copies of letters from all DMF holders (referenced in NDA 20-720) allowing the FDA to refer to these DMFs on behalf of Sankyo U.S.A. Corporation are located following this cover letter.

Sankyo U.S.A. Corporation is a wholly owned subsidiary of Sankyo Co., Ltd. By contractual agreement with Warner-Lambert, Sankyo U.S.A. Corporation has future rights to market troglitazone under our own brand name. We, therefore, are submitting this NDA to provide this for future marketing potential. Prior to marketing, we commit to supplement this NDA with any changes in Item 3 to provide for a Sankyo U.S.A. Corporation market-image tablet. In addition, the NDC numbers will be assigned in the future for these tablets.

Due to the significant therapeutic advance provided by troglitazone to insulin-taking patients with Type II diabetes, we feel a priority review for this new drug is appropriate.

If you need additional information or have any questions regarding this submission, please contact me at 212/753-3172 (FAX 212/308-2491).

Sincerely,

David L. Woodward, Ph.D.
Vice President, Development

NDA Copies
"Blue" Archive
"Tan" Medical
"Red" Chemistry
"Maroon" Field (San Juan and Newark)

"Orange" Biopharmaceutics
"Yellow" Pharmacology
"Green" Biometrics

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
Sankyo U.S.A. Corporation

DATE OF SUBMISSION
July 31, 1996

ADDRESS (Number, Street, City, State and Zip Code)
Suite 1700
780 Third Avenue
New York, N.Y. 10017

TELEPHONE NO. (Include Area Code)
(212) 753-3172

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-719

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)
troglitazone

PROPRIETARY NAME (if any)
Prelay™

CODE NAME (if any)
CI-991; CS-045; GR92132X; PD137070

CHEMICAL NAME
(±-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione)

DOSAGE FORM
Tablets

ROUTE OF ADMINISTRATION
Oral

STRENGTH(S)
200 mg, 400 mg

PROPOSED INDICATIONS FOR USE
Type II diabetes

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:
NDA 20-720
IND 32,703; 49-782 (NIH); 44,609 (K. Osei, MD, Ohio St. Univ.)
DMF 9047, 9048 (Sankyo Co., Ltd.)
DMF 721, 4164, 9314, 1016, 1466, 2880, 1933, 1941, 6684

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG

HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION
☒ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one).*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

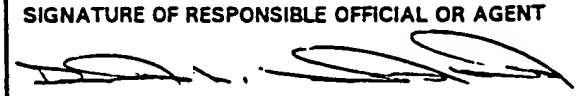
This application contains the following items: (Check all that apply)

	1. Index
●	2. Summary (21 CFR 314.50(c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50(d)(1))
	4. a. Samples (21 CFR 314.50(e)(1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
	c. Labeling (21 CFR 314.50(e)(2)(ii))
X	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3))
	7. Microbiology section (21 CFR 314.50(d)(4))
	8. Clinical data section (21 CFR 314.50(d)(5))
	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
	10. Statistical section (21 CFR 314.50(d)(6))
●	11. Case report tabulations (21 CFR 314.50(f)(1))
	12. Case reports forms (21 CFR 314.50(f)(1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
X	15. OTHER *(Specify)* NDA 20-720 is included herein by cross-reference

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
David L. Woodward, Ph.D. Vice-President, Development Sankyo U.S.A. Corporation		July 31, 1996

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
780 Third Avenue (Suite 1700) New York, N.Y. 10017	(212) 753-3172

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

EXHIBIT 11B

EXHIBIT 11B

NDA SUBMISSION LETTER FOR REZULIN™

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (313) 996-7756
Facsimile: (313) 998-2856

PARKE-DAVIS
People Who Care

Irwin G. Martin, Ph.D.
Vice President, FDA Liaison
Worldwide Regulatory Affairs

July 31, 1996

NDA 20-720
Ref. No. 1
Vol 1.1 - 1.334
Rezulin™ (troglitazone) Tablets

Re: Original New Drug Application
User Fee I.D. No. 2566

Food and Drug Administration
Document and Records Section
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir/Madam:

Pursuant to § 505(b)(1) of the FDC Act, enclosed is a new drug application (20-720) for Rezulin™ (troglitazone) Tablets. This NDA provides evidence for the use of troglitazone as an adjunct to diet in the treatment of Type II diabetes in patients who are inadequately controlled by insulin therapy.

The NDA number 20-720 was preassigned to this application on March 20, 1996. A presubmission of the rodent carcinogenicity study reports was made to this NDA on March 27, 1996 and received by the Division of Metabolism and Endocrine Drug Products on March 28, 1996. These reports, therefore, are not included in this submission.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1996 application fee ($102,000.00) has been sent to the Food and Drug Administration in care of Mellon Bank, Philadelphia, Pennsylvania on July 10, 1996. A User Fee Cover Sheet, Form FDA 3397, follows this cover letter (Attachment A).

In a letter from Dr. Sobel of the Division of Metabolism and Endocrine Drug Products on June 3, 1996 (IND 32,703), the trade name Rezulin™ was deemed acceptable.

The data contained in this NDA were developed by Parke-Davis under IND 32,703 as well as by our development partners Sankyo Co., Ltd. (Japan) and GlaxoWellcome Ltd. (U.K.). Sankyo U.S.A. Corporation conducted one study under IND 32,703 which is also contained in this NDA.

Reference is made to the letter of July 26, 1996 from Dr. Sobel, Division Director of the Division of Metabolic and Endocrine Drug Products (IND 32,703; Attachment B). As noted in Dr. Sobel's letter, the Division has waived the need for Case Report Tabulations from the clinical studies conducted by Sankyo Co., Ltd. and GlaxoWellcome, Ltd. The requirement for Case Report Forms (CRFs) from patients who withdrew from these studies due to an adverse event has also been waived, although the CRFs from patients in the GlaxoWellcome studies who withdrew due to a serious adverse event have been provided. CRFs from subjects in these trials who died have been provided.

Permission is hereby granted to Sankyo U.S.A. Corporation to include by cross reference the complete contents of this NDA, including the presubmission and any subsequent amendments to this pending NDA, in support of their application for Prelay™ (troglitazone) Tablets, NDA 20-719, which is submitted concurrently with this NDA.

Troglitazone is the first member of the thiazolidinediones class of compounds. It is an oral antihyperglycemic compound which acts primarily by treating insulin resistance. Troglitazone decreases hepatic glucose output and increases insulin dependent glucose disposal in skeletal muscle. Mechanism of action studies differentiate it from other oral antidiabetic compounds. This NDA contains clinical safety data on 3816 patients and volunteers, including 228 for over one year. Two studies of six-months duration provide evidence of efficacy in the insulin-taking Type II diabetes population. A total of 401 patients in this population have been treated with troglitazone.

Parke-Davis has met with the Division of Metabolism and Endocrine Drug Products concerning troglitazone on numerous occasions during its development. Meetings which were held to discuss the treatment of Type II diabetic patients on insulin are summarized below. Summaries of and minutes from all meetings with the agency concerning troglitazone are provided in Attachment C to this cover letter.

1) An End-of-Phase 2 meeting for insulin-taking Type II diabetic patients was held on August 2, 1995. At this meeting we provided an overview of our proposed clinical program in insulin-taking Type II diabetes patients. During subsequent conversations with the agency, it was agreed that the protocols for clinical studies 991-040 and 991-068, if successfully conducted, could provide an approvable NDA for use of troglitazone in this patient population. The final reports for these studies are enclosed with this NDA. [An End-of-Phase 2 meeting on the broader Type II diabetes indication and preclinical issues was held on August 9, 1994.]

2) A pre-NDA meeting was held on January 4, 1996. An overview of the enclosed NDA was provided at this meeting and a number of agreements were reached.

Patent and exclusivity information and the Generic Drug Enforcement Act certification are located in Item 13 and are contained in Volume 1.1 of this NDA. Please refer to the attached Form FDA 356h and NDA Index which detail the complete contents of this NDA.

Pursuant to 21 CFR 314.440, a complete copy of the Chemistry, Manufacturing and Controls section of this NDA has been sent to the FDA District Office in Newark, New Jersey. In addition, a complete copy of this section has been sent to the San Juan, Puerto Rico District Office since the drug product is manufactured at our Vega Baja, Puerto Rico facility. The drug substance is manufactured by Sankyo Co., Ltd. in Japan.

Copies of all DMF letters referenced in this NDA are located in Item 3 as well as provided immediately following this cover letter (Attachment D).

Due to the significant therapeutic advance provided by troglitazone to insulin-taking patients with Type II diabetes, we feel a priority review for this exciting new drug is appropriate.

If you need additional information or have any questions regarding this application, please contact Ms. Mary Taylor at 313/996-5000 or the undersigned. Dr. Sean Brennan may be contacted for issues related to Chemistry, Manufacturing or Controls at 313/996-7596 (FAX 313/996-7890).

Sincerely,

Irwin G. Martin, Ph.D.

IM\rm
t:\nda\20-720\073196.001

Enclosures
Attachments A - D

NDA Copies

"Blue" Archive	Vol 1.1 - 1.334
"Red" Chemistry and Labeling	Vol 1.1 - 1.23
"Yellow" Pharmacology	Vol 1.1 - 1.2, 1.24 - 1.82
"Orange" Biopharmaceutics	Vol 1.1 - 1.2, 1.83 - 1.136
"Tan" Medical	Vol 1.1 - 1.2, 1.137 - 1.215
"Green" Biometrics	Vol 1.1 - 1.2, 1.216 - 1.229
"Maroon" Field (North Brunswick) Mrs. Regina Brown	Vol 1.3 - 1.22
"Maroon" Field (San Juan) Mr. Samuel Jones/Mr. Richard Dent	Vol 1.3 - 1.22

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company	July 31, 1996
ADDRESS (Number, Street, City, State and Zip Code) 2800 Plymouth Road, P.O. Box 1047 Ann Arbor, MI 48106-1047	TELEPHONE NO. (Include Area Code) 313/996-7756
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-720

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (if any)
troglitazone	Rezulin™

CODE NAME (if any)	CHEMICAL NAME
CI-991; CS-045; GR92132X; PD137070	(±-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione)

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
●lets	Oral	200 mg, 400 mg

PROPOSED INDICATIONS FOR USE

Type II diabetes

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND 32,703
DMF 9047, 9048 (Sankyo Co., Ltd.)
DMF 721, 4164, 9314, 1016, 1466, 2880, 1933, 1941, 6684

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

● ORIGINAL APPLICATION ☐ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one).*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: (Check all that apply)

X	1. Index
X	2. Summary (21 CFR 314.50(c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50(d)(1))
	4. a. Samples (21 CFR 314.50(e)(1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
	c. Labeling (21 CFR 314.50(e)(2)(ii))
X	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3))
	7. Microbiology section (21 CFR 314.50(d)(4))
X	8. Clinical data section (21 CFR 314.50(d)(5))
	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
X	10. Statistical section (21 CFR 314.50(d)(6))
X	11. Case report tabulations (21 CFR 314.50(f)(1))
X	12. Case reports forms (21 CFR 314.50(f)(1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Irwin G. Martin, Ph.D. Vice President, FDA Liaison Worldwide Regulatory Affairs		7/31/96

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
00 Plymouth Road, P.O. Box 1047 Ann Arbor, MI 48106-1047	313/996-7756

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FORM FDA 356h(12/91)

EXHIBIT 12

EXHIBIT 12

IND LOG

CI#: 991 Sub Date: 1/30/89
Generic: Appr Date:
Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04163		Wed, Jan 04, 1989 S. Sobel, MD	Letter RE: Authorization to Submit Filings to FDA	
B04163		Mon, Jan 30, 1989 S. Sobel, MD	Letter RE: Transferring Monitoring of Clinical Investigation	
B04163	0	Mon, Jan 30, 1989	Initial IND	
B04171		Thu, Feb 09, 1989 W. Troetel J. Weber	Letter from FDA	
B04171	1	Tue, Sep 12, 1989	Protocol Amendment (New Investigators)	
B04171	2	Mon, Sep 18, 1989 S. Sobel, MD	Letter RE: New Subinvestigators)	
B04171	3	Wed, Oct 18, 1989	Protocol Amendment (Change in Protocol)	
B04171	4	Thu, Feb 01, 1990 S. Sobel, MD	Letter RE: Increase Dosing Period	
B04171	5	Fri, Apr 06, 1990 S. Sobel, MD	Letter RE: Lower of Plasma Glucose Levels	
B04171	6	Mon, Apr 16, 1990	Annual Report	
B04171	7	Mon, Jul 09, 1990 S. Sobel, MD	Letter RE: Updated Summary and Clinical Data Information	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04171	8	Fri, Oct 12, 1990 S. Sobel, MD	Letter RE: Transfer of IND Sponsorship	
B04171	9	Tue, Nov 20, 1990 S. Sobel, MD	Letter RE: Response to FDA Request for Information	
B04172	10	Tue, Apr 23, 1991 S. Sobel, MD	Letter RE: Chemistry/Microbiology	
B04172	11	Wed, Apr 24, 1991	Annual Report	
B04172	12	Fri, Apr 26, 1991 S. Sobel, MD	Letter RE: Transfer of IND	
B04173	13	Mon, May 13, 1991 S. Sobel, MD I. Martin	Letter RE: Transference of IND	
B04173		Mon, May 20, 1991 I. Martin E. Nakajima, Ph.D.	Memo RE: Type I DMF 9047	
B04173		Mon, May 20, 1991 I. Martin E. Nakajima, Ph.D.	Memo RE: Type II DMF 9047	
B04173		Tue, May 21, 1991	Minutes of FDA Meeting	
B04173	14	Fri, May 24, 1991 S. Sobel, MD I. Martin, Ph.D.	Letter RE: Information Amendment (Chemistry)	
B04173	15	Fri, Jun 07, 1991 S. Sobel, MD. I. Martin, Ph.D.	Letter RE: Information Amendment (Clinical) to IND 32,703 for CI-991 tablets	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04173		Wed, Jun 12, 1991	Memo RE: June 3, 1991 Meeting Minutes	
		L. Spivey		
		L.E. Weissberger		
B04173	16	Thu, Jun 13, 1991	Response to FDA RE: Request for Information	
		S.Sobel, MD		
		I. Martin, Ph.D.		
B04173	17	Thu, Jun 20, 1991	Letter RE: General Correspondence	
		S. Sobel, MD		
		I. Martin		
B04173	18	Thu, Jul 18, 1991	Letter RE: Information Amendment (Clinical)	
		S. Sobel, MD		
		I. Martin		
B04174	19	Wed, Jul 31, 1991	IB Update	
B04174	20	Wed, Sep 04, 1991	Protocol Amendment (New Investigators)	
B04175	21	Fri, Sep 06, 1991	Information Amendment (Pharmacology/Toxicology)	
B04176	22	Tue, Oct 01, 1991	Protocol Amendments (New Investigators)	
B04176		Wed, Oct 02, 1991	FDA Letter RE: Sponsorship Transfer	
		I. Martin		
		S. Sobel		
B04176	23	Fri, Nov 01, 1991	Letter RE: Information Amendment Letter RE: Information Amendment (CLinical)	
		S. Sobel, MD		
		I. Martin		
B04176	24	Thu, Dec 12, 1991	Information Amendment (Clinical)	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04176	25	Wed, Jan 08, 1992		Protocol Amendment (New Investigators/Change in Protocol)
B04176	26	Wed, Jan 08, 1992		Information Amendment (Pharmacology/Toxicology)
B04176	27	Fri, Jan 17, 1992 S. Sobel I. Martin	Letter RE: Information Amendment (Chemistry) and Protocol Amendment (New Investigator)	
B04176	28	Mon, Jan 27, 1992		Protocol Amendment (New Investigator)
B04176	29	Wed, Feb 12, 1992 S. Sobel I. Martin	Letter RE: Information Amendment	
B04176	30	Mon, Mar 16, 1992	Letter RE: Information Amendment (Pharmacology/Toxicology)	
B04177	31	Fri, Mar 27, 1992 S. Sobel I. Martin	Letter RE: Information Amendment	
B04178	32	Tue, Apr 21, 1992 S. Sobel I. Martin	Letter RE: Information Amendments	
B04178	33	Tue, Apr 28, 1992		Annual Report
B04178	34	Fri, May 15, 1992		Information Amendments (Pharmacology/Toxicology)
B04178	35	Thu, May 21, 1992		Protocol Amendment (New Investigators)

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B04178	36	Mon, Jun 01, 1992 S. Sobel I. Martin	Letter RE: General Correspondence
B04178	37	Fri, Jun 05, 1992	Protocol Amendments (New Investigators/Change in Protocol)
B04178	38	Tue, Jun 09, 1992	Information Amendment (Clinical)
B04178	39	Fri, Jun 12, 1992 S. Sobel I. Martin	Letter RE: General Correspondence
B04178	40	Tue, Jun 16, 1992	Information Amendment (Pharmacology/Toxicology)
B04178	41	Tue, Aug 04, 1992 S. Sobel I. Martin	Letter RE: Information Amendment: CMC
B04178	42	Thu, Aug 27, 1992	Information Amendment (Pharmacology/Toxicology)
B04178	43	Tue, Sep 29, 1992	Letter RE: Information Amendment (Pharmacology/Toxicology)
B04179	44	Mon, Oct 12, 1992	Information Amendment (Pharmacology/Toxicology)
B04179		Tue, Oct 27, 1992	FDA Letter RE: Refer to IND 32,703
B04179	45	Tue, Nov 24, 1992	Information Amendment (Pharmacology/Toxicology)

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B04180	46	Wed, Nov 25, 1992	Protocol Amendment (New Protocol)
B04180	47	Tue, Dec 01, 1992	Protocol Amendment (New Protocol)
B04180	48	Fri, Dec 11, 1992 S. Sobel I. Martin	General Correspondence
B04180	49	Mon, Dec 28, 1992	Protocol Amendment (Change in Protocol)
B04180		Thu, Jan 07, 1993 I. Martin S. Sobel	FDA Letter RE: Comment Regarding Toxicology Studies
B04180	50	Mon, Jan 18, 1993	Protocol Amendment (New Investigators/Change in Protocol)
B04180	51	Mon, Jan 18, 1993	Protocol Amendment (New Protocol)
B04180	52	Wed, Jan 20, 1993	Protocol Amendment (New Protocol)
B04180	53	Tue, Feb 02, 1993	Protocol Amendment (New Investigators)
B04180	54	Tue, Feb 02, 1993 S. Sobel I. Martin	General Correspondence
B04181	55	Tue, Feb 16, 1993 S. Sobel Hards/Martin	General Correspondence

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04181	56	Mon, Feb 22, 1993	Protocol Amendment (Change in Protocol)
B04181	57	Wed, Feb 24, 1993	Protocol Amendment (New Investigators)
B04181		Fri, Feb 26, 1993 Ann Hards	FDA/P-D Meeting Minutes (23-Feb-93)
B04181	58	Mon, Mar 01, 1993	Protocol Amendment (Change in Protocol)
B04181	59	Wed, Mar 03, 1993	Protocol Amendment (New Investigator)
B04181	60	Mon, Mar 15, 1993	Protocol Amendment (New Investigators)
B04181	61	Tue, Mar 16, 1993	Minutes of FDA/P-D Meeting
B04181	62	Thu, Mar 25, 1993	Chemistry, Manufacturing, and Controls
B04181	63	Fri, Mar 26, 1993	General Correspondence
B04181	64	Fri, Apr 02, 1993	Protocol Amendment (New Investigators)
B04181	65	Mon, Apr 05, 1993	Letter RE: Closing FDA Master File 535

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04181		Wed, Apr 07, 1993 I. Martin S. Sobel	FDA Letter
B04181	66	Tue, Apr 13, 1993	Protocol Amendment (New Investigator)
B04181	67	Thu, Apr 15, 1993 S. Sobel I. Martin	General Correspondence
B04181	68	Tue, Apr 20, 1993	Protocol Amendments (New Investigator & Change in Protocol)
B05726	69	Tue, May 04, 1993 S. Sobel I. Martin	Response to FDA Request for Information
B05726	70	Wed, May 05, 1993 S. Sobel I. Martin	Information Amendment (Pharmacology/Toxicology)
B05726	71	Fri, May 07, 1993	Protocol Amendment (Change in Protocol)
B05726	72	Fri, May 07, 1993	IND Safety Report/Initial Written Report
B05726	73	Mon, May 17, 1993 S. Sobel I. Martin	Letter RE: Minutes of 26-Apr-Meeting
B05726		Tue, May 18, 1993	Minutes of FDA Meeting (26-Apr-93)
B05726	74	Fri, May 21, 1993 S. Sobel I. Martin	Letter RE: Information Amendment (Pharmacology/Toxicology & Clinical)

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B05726	75	Wed, May 26, 1993	Letter RE: General Correspondence	
B05726	76	Tue, Jun 01, 1993	Protocol Amendment (New Investigators/Change in Protocol)	
B05727	77	Tue, Jun 08, 1993	Information Amendment (Pharmacology/Toxicology & Clinical)	
B05921	78	Fri, Jun 18, 1993	Protocol Amendment (Changes in Protocol)	
B05921	79	Fri, Jun 25, 1993	IND Safety Report: Initial Written Report	
B05921	80	Fri, Jun 25, 1993	Annual Report	
B05921	81	Wed, Jun 30, 1993	IND Safety Report: Initial Written Report	
B05921		Wed, Jul 07, 1993	FDA Letter RE: Submission dated 4-May-93	
B05921	82	Thu, Jul 08, 1993	Protocol Amendment (Change in Protocol & New Investigators)	
B05921	83	Fri, Jul 09, 1993	Information Amendment (Clinical)	
B05921	84	Thu, Jul 15, 1993	Information Amendment (Pharmacology/Toxicology & Clinical)	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B06146	85	Mon, Jul 19, 1993	IND Safety Report: Initial Written Report
B06146	86	Mon, Jul 19, 1993	General Correspondence
B06146	87	Tue, Jul 27, 1993	Information Amendment (Clinical)
B06146	88	Tue, Aug 10, 1993	Information Amendment (Pharmacology/Toxicology & Clinical)
B06146	89	Fri, Aug 13, 1993	Response to FDA Request for Information
B06146	90	Fri, Aug 13, 1993	IND Safety Report: 10 Day Report
B06146	91	Mon, Aug 16, 1993	Information Amendment (Clinical)
B06146	92	Tue, Aug 24, 1993	IND Safety Report - Follow-Up
B06146	93	Wed, Aug 25, 1993	Information Amendment: Clinical
		S. Sobel	
		I. Martin	
B06146	93	Wed, Aug 25, 1993	Information Amendment (Clinical)
B06146	94	Wed, Sep 01, 1993	Protocol Amendments: Change in Protocol
		S. Sobel	
		I. Martin	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06284	95	Fri, Sep 17, 1993 S. Sobel I. Martin	IND Safety Report: Initial Written Report
B06284	96	Tue, Sep 21, 1993 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology
B06284	97	Thu, Sep 30, 1993 S. Sobel I. Martin	Protocol Amendment: New Protocol
B06284	98	Fri, Oct 15, 1993 S. Sobel I. Martin	General Correspondence
B06284	99	Thu, Oct 21, 1993 S. Sobel I. Martin	Protocol Amendments: New Investigator/Change in Protocol
B06378	100	Thu, Oct 21, 1993 S. Sobel I. Martin	Information Amendments: Pharmacology-Toxicology/Clinical
B06378	101	Wed, Oct 27, 1993 S. Sobel Irwin Martin	Protocol Amendments: New Protocol/Change in Protocol
B06378		Tue, Nov 02, 1993 S. Sobel I. Martin	Minutes
B06378	102	Wed, Nov 03, 1993 S. Sobel I. Martin	Protocol Amendment: Change in Protocol
B06378	103	Fri, Nov 05, 1993 S. Sobel I. Martin	General Corresopndence: Minutes of November 2, 1993 Meeting
B06378	104	Wed, Nov 10, 1993 S. Sobel I. Martin	Information Amendments: Pharm/Tox/Clinical

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B06378	105	Fri, Nov 19, 1993 S. Sobel I. Martin	Protocol Amendment: New Investigator
B06511		Mon, Nov 22, 1993 I. Martin S. Sobel	FDA letter reference response to FDA Request for Information on 7/7/93
B06511		Mon, Nov 22, 1993 I. Martin S. Sobel	FDA letter Request for Information
B06511	106	Mon, Nov 22, 1993 S. Sobel D. Furlano	CMC Amendment: Drug Substance Analytical Method Update
B06511	107	Wed, Dec 01, 1993 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report
B06511	108	Fri, Dec 03, 1993 S. Sobel I. Martin	Response to FDA Request for Information
B06511	109	Tue, Dec 07, 1993 S. Sobel I. Martin	Information Amendment: Pharmacology/Toxicology
B06511	110	Mon, Dec 13, 1993 S. Sobel D. Furlano	Information Amendment: Chemistry, Manufacturing and Controls
B06511	111	Wed, Dec 22, 1993 S. Sobel D. Furlano	Information Amendment: Chemistry (DMF Update Notification)
B06511	112	Tue, Dec 28, 1993 S. Sobel A. Hards	Information Amendment: Clinical
B06551	113	Thu, Jan 06, 1994 S. Sobel I. Martin	IND Safety Report: Initial Written Report

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06551	114	Wed, Jan 12, 1994 S. Sobel I. Martin	Protocol Amendments: New Protocol/Change in Protocol	
B06551	115	Mon, Jan 17, 1994 S. Sobel I. Martin	Information Amendments: Clinical	
B06551	116	Wed, Feb 09, 1994 S. Sobel I. Martin	Information Amendment: Pharmacology/Toxicology	
B06551	117	Fri, Feb 11, 1994 S. Sobel I. Martin	Response to FDA Request for Information	
B06551	118	Fri, Mar 04, 1994 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology	
B06551	119	Fri, Mar 11, 1994 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report	
B06551	120	Thu, Mar 31, 1994 S. Sobel I. Martin	Protocol Amendments: Change in Protocol	
B06551	121	Tue, Apr 12, 1994 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report	
B06551	122	Fri, Apr 29, 1994 S. Sobel I Martin	Information Amendments: Clinical	
B06551	123	Wed, May 04, 1994 S. Sobel D. Furlano	Information Amendment: Chemistry (DMF Update Notification)	
B06551	125	Thu, May 12, 1994 S. Sobel D. Furlano	Information Amendment: CMC Update - Specifications and Tests for Bulk Drug Substance	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06993	124	Thu, May 12, 1994 S. Sobel I. Martin		Information Amendments: Pharmacology/Toxicology/Clinical
B06993		Tue, May 17, 1994 I. Martin A. Itoh		Letter from Sankyo: Regarding move to new headquarters
B06993	126	Wed, May 18, 1994 S. Sobel I. Martin		Protocol Amendment: Change in Protocol
B06993	127	Tue, May 31, 1994 S. Sobel I. Martin		General Correspondence: Request for End-of-Phase 2 Meeting
B07017	128	Wed, Jun 01, 1994 S. Sobel M. Taylor		Information Amendments: Pharmacology/Toxicology/Clinical
B07055		Mon, Jun 20, 1994 I. Martin S. Sobel		Letter from FDA: Regarding Research Reports
B07055	129	Wed, Jun 29, 1994 S. Sobel I. Martin		Information Amendment: Pharmacology/Toxicology
B07055	130	Thu, Jul 07, 1994 S. Sobel I. Martin		Protocol Amendment: New Protocol
B07055	131	Thu, Jul 07, 1994 S. Sobel D. Furlano		Information Amendment: Chemistry, Manufacturing and Controls
B07055		Thu, Jul 14, 1994 M. Limoli I. Martin		Drug Export Application
B07055	132	Tue, Jul 19, 1994 S. Sobel I. Martin		Annual Report

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B07055	133	Fri, Jul 22, 1994 S. Sobel I. Martin	Protocol Amendment: New Protocol
B07102	134	Wed, Jul 27, 1994 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology
B07203	135	Mon, Aug 08, 1994 S. Sobel I. Martin	Protocol Amendments: Change in Protocol
B07203		Tue, Aug 09, 1994 Parke-Davis J. Short	Memorandum of End-of-Phase 2 Meeting
B07203	136	Tue, Aug 23, 1994 S. Sobel I. Martin	General Correspondence: Letter of Authorization
B07203	137	Wed, Aug 24, 1994 S. Sobel I. Martin	Protocol Amendment: New Protocol
B07203	138	Fri, Aug 26, 1994 S. Sobel I. Martin	Protocol Amendment: New Protocol
B07203		Tue, Aug 30, 1994 I. Martin S. Sobel	Letter from FDA: Annual Report
B07203	139	Thu, Sep 08, 1994 S. Sobel I. Martin	General Correspondence: End-of-Phase 2 Meeting Minutes
B07203	140	Fri, Sep 09, 1994 S. Sobel I. Martin	Protocol Amendment: New Investigator
B07203	141	Wed, Sep 21, 1994 S. Sobel I. Martin	Protocol Amendments: New Protocol/New Investigator

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Contents/Report No./	Report No.
B07203	142	Fri, Sep 30, 1994 S. Sobel, M.D. I. Martin	Protocol Amendment: New Investigator	
B07203		Tue, Oct 04, 1994 J. Short I. Martin	Response to FDA Request for Information	
B07203	143	Tue, Oct 04, 1994 S. Sobel, M.D. D. Furlano	Information Amendment: Chemistry, Manufacturing and Controls	
B07203		Tue, Oct 25, 1994 I. Martin C.M. Limoli	Letter from FDA	
B07203	146	Wed, Oct 26, 1994 S. Sobel I. Martin	Protocol Amendment: New Protocol	
B07203	145	Wed, Oct 26, 1994 S. Sobel I. Martin	General Correspondence: Suspended Enrollment	
B07203	147	Thu, Oct 27, 1994	Protocol Amendment: New Protocol	
B07203	144	Thu, Nov 17, 1994 S. Sobel I. Martin	Information Amendment: Clinical	
B07258	149	Tue, Nov 29, 1994 S.Sobel I. Martin	General Correspondence: 52-Week Monkey Study Summary	
B07258	148	Tue, Nov 29, 1994 S. Sobel D. Furlano	Information Amendment: Chemistry (DMF Update Notification)	
B07258	150	Thu, Dec 08, 1994 S. Sobel I. Martin	Protocol Amendment: Change in Protocol	

SubType: IND

Cl#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Contents/Report No./	Report No.
B07258	151	Thu, Dec 22, 1994 S. Sobel I. Martin	IND Safety Report: Initial Written Report	
B07258	152	Thu, Jan 05, 1995 S. Sobel I. Martin	Protocol Amendments: New Protocol/General Correspondence	
B07258	153	Fri, Jan 06, 1995 S. Sobel D. Furlano	Information Amendment: CMC	
B07258	154	Mon, Jan 16, 1995 S. Sobel I. Martin	Protocol Amendment: General Correspondence	
B07424	155	Tue, Jan 31, 1995 S. Sobel I. Martin	Protocol Amendment: New Protocol/New Investigators/Change in Protocol	
B07424	156	Mon, Feb 06, 1995 S. Sobel D. Furlano	Information Amendment: Chemistry (DMF Update Notification)	
B07424	157	Fri, Feb 17, 1995 S. Sobel I. Martin	Protocol Amendment: New Protocol	
B07496	158	Tue, Feb 21, 1995 S. Sobel I. Martin	Protocol Amendment: New Investigators	
B07496		Tue, Feb 28, 1995 I. Martin S. Sobel	Letter from FDA	
B07496	159	Wed, Mar 01, 1995 S. Sobel I. Martin	IND Safety Report: Initial Written Report	
B07496	160	Fri, Mar 03, 1995 S. Sobel I. Martin	Protocol Amendment: New Protocol	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B07496	161	Tue, Mar 07, 1995 S. Sobel I. Martin	Protocol Amendment: Change in Protocol
B07609	162	Tue, Apr 04, 1995 S. Sobel I. Martin	Informaiton Amendments: Pharmacology/Toxicology/Clinical
B07604	163	Wed, Apr 05, 1995 S. Sobel I. Martin	Protocol Amendments: New Investigators/Change in Protocol
B07646	164	Wed, Apr 12, 1995 S. Sobel I. Martin	Protocol Amendment: New protocol, New Investigators, Change in Protocol
B07604	165	Fri, Apr 21, 1995 S. Sobel I. Martin	Protocol Amendment, New Protocol
	166	Mon, Apr 24, 1995	Protocol Amendment: Change in Protocol
B07604	166	Mon, Apr 24, 1995 S. Sobel I. Martin	Protocol Amendment: Change in Protocol
B07677	167	Fri, Apr 28, 1995 S. Sobel S. Brennan	Information Amendment: Chemistry, Manufacturing and Controls
B07677	168	Wed, May 03, 1995 S. Sobel I. Martin	General Correspondence
B07677	169	Wed, May 31, 1995 S. Sobel I. Martin	Request for FDA Meeting
B07677	0	Mon, Jun 05, 1995 Mr. J. Short M. Taylor	General Correspondence

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
	170	Wed, Jun 07, 1995 S. Sobel I. Martin	New Protocol: 991-057-001
	172	Thu, Jun 15, 1995 S. Sobel I. Martin	Information Amendments: Pharmcology/Toxicology & Clinical
B10131	171	Mon, Jun 19, 1995 S. Sobel I. Martin	RR 744-00178, 745-02254, 764-02308, 764-02345...
B10134	173	Fri, Jul 07, 1995 S. Sobel I. Martin	IND Safety Report
B10134	174	Wed, Jul 12, 1995 S. Sobel I. Martin	Annual Report
B10134	175	Tue, Aug 08, 1995 S. Sobel I. Martin	IND Safety Report
B10134	176	Tue, Aug 08, 1995 S. Sobel I. Martin	IND Safety Report
B10320	177	Mon, Aug 14, 1995 S. Sobel I. Martin	Submission of 30 Research Reports
B10298	178	Mon, Aug 14, 1995 S. Sobel I. Martin	New Investigators
B10298	179	Tue, Aug 15, 1995 S. Sobel I. Martin	New Protocol 991-068 & Amendment 1
B10298	180	Thu, Aug 24, 1995 S. Sobel I. Martin	New Investigators

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Contents/Report No./	Report No.
B10298	181	Mon, Aug 28, 1995 S. Sobel I. Martin	New Protocol	
B10298	182	Wed, Aug 30, 1995 S. Sobel I. Martin	New Protocol	
B10521	183	Tue, Sep 05, 1995 S. Sobel I. Martin	IND Safety Report	
B10521	185	Mon, Sep 11, 1995 S. Sobel I. Martin	IND Safety Report	
B10521	184	Thu, Sep 14, 1995 S. Sobel I. Martin	New Investigators	
B10521	186	Thu, Sep 14, 1995 S. Sobel I. Martin	IND Safety Report	
B10521	187	Fri, Sep 15, 1995 S. Sobel I. Martin	IND Safety Report	
B10521	188	Fri, Sep 22, 1995 S. Sobel I. Martin	Response to FDA Request for Information	
B10521	189	Tue, Sep 26, 1995 S. Sobel I. Martin	IND Safety Update	
B10521	190	Wed, Sep 27, 1995 S. Sobel I. Martin	IND Safety Report: Initial Written Report	
B10521	191	Mon, Oct 02, 1995 S. Sobel I. Martin	IND Safety Report: Follow-Up to a Written Report	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B10521	192	Wed, Oct 04, 1995	S. Sobel	Information Amendment: Pharmacology/Tox
			I. Martin	
B10726	193	Wed, Oct 04, 1995	S. Sobel	Information Amendment: Pharmacology/Tox
			I. Martin	
	194	Tue, Oct 17, 1995	S. Sobel	IND Safety Report: Initial Written Report
			I. Martin	
B10842	195	Tue, Oct 24, 1995	S. Sobel	General Correspondence
			I. Martin	
B10842	196	Tue, Oct 24, 1995	S. Sobel	General Correspondence: Pre-NDA Meeting Request
			102495.196	
B10842	197	Tue, Oct 24, 1995	S. Sobel	IND Safety Report: Initial Written Report
			I. Martin	
B10842	198	Mon, Oct 30, 1995	S. Sobel	Protocol Amendments: Change in Protocol
			I. Martin	
B10842	199	Thu, Nov 02, 1995	S. Sobel	Information Amendment: Pharmacology/Tox
			I. Martin	
B10842	200	Thu, Nov 02, 1995	S. Sobel	Information Amendments: Clinical
			I. Martin	
B11010	201	Wed, Nov 08, 1995	S. Sobel	Information Amendment: Pharmacology/Tox
			I. Martin	
B10992	202	Thu, Nov 09, 1995	S. Sobel	IND Safety Report: Initial Written Report
			I. Martin	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B10992	203	Thu, Nov 09, 1995	Information Amendment: CMC
		S. Sobel	
		S. Brennan	
B10992	204	Tue, Nov 14, 1995	General Correspondence: Proposal for Trade Name
		S. Sobel	
		I. Martin	
B10992	206	Tue, Nov 21, 1995	Protocol Amendments: New Protocol
		S. Sobel	
		I. Martin	
B10992	207	Tue, Nov 21, 1995	IND Safety Report: Follow-Up to a Written Report
		S. Sobel	
		I. Martin	
B10992	208	Wed, Nov 22, 1995	IND Safety Report: Follow-Up No. 2 to a Written Report
		S. Sobel	
		I . Martin	
B10992	209	Tue, Nov 28, 1995	IND Safety Report: Follow-Up to a Written Report
		S. Sobel	
		I. Martin	
B10992		Tue, Nov 28, 1995	FDA's Reply
		I. Martin	
		G. Troendle	
B10992	210	Fri, Dec 01, 1995	Protocol Amendments: New Protocol
		S. Sobel	
		I. Martin	
B10992	211	Mon, Dec 04, 1995	Protocol Amendments: New Protocol
		S. Sobel	
		I. Martin	
B11677	212	Tue, Dec 12, 1995	Information Amendments: Pharmacology/Tox & Clinical
		S. Sobel	
		I. Martin	
B11677	213	Thu, Dec 14, 1995	Information Amendments: Clinical
		S. Sobel	
		I. Martin	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B11844	214	Thu, Dec 21, 1995 S. Sobel I. Martin	Protocol Amendments: New Protocol and General Correspondence
B11844	215	Thu, Dec 21, 1995 S. Sobel I. Martin	General Correspondence: Mock ISS and ISE
B11844	216	Fri, Dec 22, 1995 S. Sobel I. Martin	Protocol Amendments: New Protocol
B11844	217	Thu, Dec 28, 1995 S. Sobel I. Martin	Protocol Amendments: New Investigators
B11844	218	Fri, Jan 12, 1996 S. Sobel I. Martin	General Correspondence
B12336	219	Mon, Jan 15, 1996 S. Sobel I. Martin	Information Amendment: Clinical, Pharmacology/Toxicology
B12569	220	Mon, Jan 22, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol
B12569	221	Mon, Jan 22, 1996 S. Sobel I. Martin	IND Safety Report: Initial Written Report
B12569	222	Wed, Jan 24, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol
B12569	223	Fri, Jan 26, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report
B12569	224	Tue, Jan 30, 1996 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B12569	225	Tue, Jan 30, 1996 S. Sobel I. Martin	Protocol Amendment: New Protocol	
B12569	226	Wed, Jan 31, 1996 S. Sobel I. Martin	IND Safety Report: Initial Written Report	
B12569	227	Thu, Feb 01, 1996 S. Sobel I. Martin	Information Amendment: Clinical	
B12569	228	Mon, Feb 05, 1996 S. Sobel I. Martin	General Correspondence: Pre-NDA Meeting Minutes	
B12569	229	Tue, Feb 06, 1996 S. Sobel I. Martin	IND Safety Report: Initial Written Report	
B13013	230	Fri, Feb 09, 1996 S. Sobel I. Martin	Information Amendments: Clinical and Pharmacology/Toxicology	
B12569	232	Wed, Feb 14, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol	
B12569	231	Wed, Feb 14, 1996 S. Sobel I. Martin	Response to FDA Request for Information	
B13015	233	Wed, Feb 21, 1996 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology	
B13015	234	Wed, Feb 21, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol	
B13015	235	Wed, Feb 21, 1996 S. Sobel I. Martin	General Correspondence: Request for Meeting	

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B13015	0	Thu, Feb 22, 1996 R. Whitcomb G. Elder-Leak, NIH	National Institute of Health's Follow-up Correspondence
B13015	236	Tue, Feb 27, 1996 S. Sobel I. Martin	Information Amendment: Clinical
B13015	237	Tue, Feb 27, 1996 S. Sobel I. Martin	Information Amendment: Pharmacology/Toxicology
B13015	0	Mon, Mar 04, 1996 A. Jordan I. Martin	Desk Copy
B13015	0	Mon, Mar 04, 1996 PD Distribution I. Martin	Meeting Minutes
B13015	238	Tue, Mar 12, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up to a written report
B13015	239	Wed, Mar 13, 1996 S. Sobel I. Martin	Protocol Amendments: Changes in Protocol, New Investigator
B13827	240	Thu, Mar 21, 1996 S. Sobel I. Martin	Information Amendments: Pharmacology/Toxicology and Clinical
B14043		Fri, Mar 22, 1996 I. Martin G. Troendle	FDA's reply to Serial No. 237
B14043	241	Tue, Mar 26, 1996 S. Sobel I. Martin	Information Amendment: Clinical
B14043	243	Wed, Mar 27, 1996 S. Sobel I. Martin	General Correspondence

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B14043	242	Mon, Apr 01, 1996 S. Sobel I. Martin	General Correspondence: Pre-NDA Meeting Information
B14043	244	Tue, Apr 02, 1996 S. Sobel I. Martin	General Correspondence
B14043	245	Tue, Apr 09, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol, New Investigators
B14043	246	Wed, Apr 10, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report
B14043	247	Wed, Apr 10, 1996 S. Sobel I. Martin	Protocol Amendment: New Protocol
B14034	248	Fri, Apr 19, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report
B14043	249	Tue, Apr 23, 1996 S. Sobel I. Martin	Protocol Amendments: New Protocol, Change in Procol, New Investigators
B14732	250	Tue, Apr 23, 1996 S. Sobel I. Martin	Response to FDA Request for Information
B14732	251	Tue, May 14, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up to a Written Report
B14732	252	Tue, May 28, 1996 S. Sobel I. Martin	Protocol Amendment: Change in Protocol, New Investigators
B14732	253	Thu, May 30, 1996 S. Sobel I. Martin	IND Safety Report: Follow-up No. 2 to a Written Report

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B14732	254	Thu, May 30, 1996		Protocol Amendment, New Protocol, New Investigators
		S. Sobel		
		I. Martin		
B14732		Mon, Jun 03, 1996		FDA's Reply
		I. Martin		
		S. Sobel		
B14732	255	Mon, Jun 17, 1996		Protocol Amendment: New Protocol
		S. Sobel		
		I. Martin		
B14732	256	Mon, Jun 24, 1996		General Correspondence
		S. Sobel		
		I. Martin		
B14732	257	Fri, Jun 28, 1996		Protocol Amendment: New Protocol
		S. Sobel		
		I. Martin		
B20038	259	Wed, Jul 10, 1996		Annual Report
		S. Sobel		
		I. Martin		
B20038	260	Thu, Jul 11, 1996		General Correspondence
		S. Sobel		
		I. Martin		
B20038	261	Thu, Jul 11, 1996		General Correspondence: Meeting Minutes
		S. Sobel		
		I. Martin		
B20038		Fri, Jul 26, 1996		FDA's Reply
		I. Martin		
		S. Sobel		
B20038	262	Mon, Jul 29, 1996		Protocol Amendment: New Protocol
		S. Sobel		
		I. Martin		
B20038	263	Mon, Aug 26, 1996		IND Safety Report: Initial Written Report
		S. Sobel		
		I. Martin		

SubType: IND

CI#: 991 Sub Date: 1/30/89

Generic: Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B20038	264	Thu, Aug 29, 1996		Protocol Amendment: New Protocol, Change in Protocol
		S. Sobel		
		I. Martin		
B20038	265	Tue, Sep 10, 1996		IND Safety Report: Follow-up to a written report
		S. Sobel		
		I. Martin		
B22145	266	Fri, Sep 13, 1996		Protocol Amendment: New Protocol
		S. Sobel		
		M. Taylor		
B22145	267	Mon, Sep 16, 1996		IND Safety Report: Follow-up to a Written Report
		S. Sobel		
		M. Tyler		
B22145		Thu, Sep 19, 1996		Clinical Review
		Mary E. Taylor		
		Gloria Troendle		
B22145	268	Fri, Sep 27, 1996		General Correspondence: Literature
		S. Sobel		
		M. Tayler		
B22145	269	Tue, Oct 01, 1996		Protocol Amendments: Change in Protocols, New Investigators
		S. Sobel		
		M. Taylor		
B22145	270	Fri, Oct 18, 1996		Protocol Amendment: New Investigators, Change in Protocol
		S. Sobel		
		M. Taylor		
B22526	271	Wed, Oct 30, 1996		Protocol Amendment: New Protocol
		S. Sobel		
		M. Taylor		
B22526	272	Fri, Nov 01, 1996		IND Safety Update: Follow-up to a Written Report
		S. Sobel		
		M. Taylor		
B22526	273	Wed, Nov 06, 1996		Protocol Amendment: New Investigators
		S. Sobel		
		M. Taylor		

SubType: IND

CI#: 991 | Sub Date: 1/30/89

Generic: | Appr Date:

Product Name: Troglitazone Tablets

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B22526	274	Fri, Nov 15, 1996 S. Sobel M. Taylor		IND Safety Report: Second Follow-up to an Initial Written Report
B22526	275	Fri, Nov 22, 1996 S. Sobel M. Taylor		Protocol Amendment: New Investigators
B22526	276	Mon, Nov 25, 1996 S. Sobel M. Taylor		General Correspondence: Draft Protocol for Review

EXHIBIT 13

EXHIBIT 13

NDA LOG

SubType: NDA

CI#: 991 Sub Date: 7/31/96

Generic: Appr Date:

Product Name: Troglitazone

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B14151	0	Wed, Mar 27, 1996		Presubmission NDA
		S. Sobel		
		I. Martin		
B14741		Thu, Apr 04, 1996		Pre-submission Receipt
		I. Martin		
		E. Galliers		
B14741	0	Wed, May 01, 1996		Desk Copy of Presubmission NDA
		J. Webber		
		I. Martin		
B14741		Tue, Jul 16, 1996		7/2/96 Meeting Minutes
		Central Labeling Co		
		I. Martin		
B14741		Wed, Jul 31, 1996		Desk Copy Action Package
		E. Galliers, FDA		
		M. Taylor		
B14741		Wed, Jul 31, 1996		Pivotal Study Information
		G. Turner, FDA		
		M. Taylor		
B20352	1	Wed, Jul 31, 1996		Original New Drug Application
		FDA		
		I. Martin		
B20973	0	Thu, Aug 01, 1996		Submission of Electronic Data
		D. Marticello, Ph.D.		
		M. Taylor		
B20973		Mon, Aug 05, 1996		Acknowledgement of NDA submission.
		I. Martin		
		E. Galliers		
B20973		Mon, Aug 12, 1996		Copy of Summary Volume of the NDA.
		A. Itoh		
		M. Taylor		
B21244	2	Thu, Aug 15, 1996		Request for Information.
		S. Sobel		
		M. Taylor		

SubType: NDA

CI#: 991 Sub Date: 7/31/96

Generic: Appr Date:

Product Name: Troglitazone

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B21244	3	Thu, Aug 22, 1996 S. Sobel I. Martin	Copy of Case Report Forms
B21785		Thu, Aug 22, 1996 G. Turner I. Martin	Request for Case Report Forms
B21244		Thu, Aug 22, 1996 Central Labeling Co I. Martin	Meeting Minutes
B21244	4	Tue, Aug 27, 1996 S. Sobel I. Martin	NDA Review Status
B21244	0	Wed, Aug 28, 1996 G. Turner I. Martin	Request for Case Report Forms - Additional Information
B21244	5	Thu, Aug 29, 1996 S. Sobel I. Martin	NDA Review Status
B21244	6	Thu, Sep 05, 1996 S. Sobel I. Martin	NDA Review Status
B21244		Mon, Sep 09, 1996 Charles E. Rothwell C.T. Viswanathan	Carcinogenicity Reports for Troglitazone
	7	Thu, Sep 12, 1996 S. Sobel I. Martin	Reference is made to our pending NDA for Rezulin™
B21244	8	Mon, Sep 16, 1996 S. Sobel I. Martin	Response to FDA Request for Information
B21244		Tue, Sep 17, 1996 Irwin G. Martin Solomon Sobel	Priority Review

SubType: NDA

CI#: 991 Sub Date: 7/31/96

Generic: Appr Date:

Product Name: Troglitazone

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
	9	Tue, Sep 24, 1996 S. Sobel I. Martin	Electronic Data Sets	
B22334	10	Tue, Oct 01, 1996 S. Sobel S. Brennan	Letter of Authorization	
B22334	11	Wed, Oct 02, 1996 S. Sobel I. Martin	Request for Additional Information	
B22334		Wed, Oct 02, 1996 M. Fossler M. Taylor	Desk Copy	
B22334	12	Fri, Oct 04, 1996 S. Sobel S. Brennan	Minor Amendment - CMC	
B22334	0	Mon, Oct 07, 1996 H. Rhee M. Taylor	Desk Copy of Two Research Reports	
B22334		Wed, Oct 09, 1996 Distribution W. Merino	Meeting with Drs. Bilstad and Sobel	
B22334		Wed, Oct 09, 1996 Irwin G. Martin Solomon Sobel	Deficiencies in the Environmental Assessments of 20-720 and 20-719	
B22363	13	Thu, Oct 17, 1996 S. Sobel I. Martin	Requested Study Reports	
B22364	14	Fri, Oct 18, 1996 S Sobel I Martin	Updated Information	
B22364	15	Mon, Oct 28, 1996 S. Sobel I. Martin	Labeling Safety Update	

SubType: NDA

CI#: 991 Sub Date: 7/31/96

Generic: Appr Date:

Product Name: Troglitazone

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B22364	16	Fri, Nov 01, 1996	Minor Amendment Revised Confidential Environmental Assessment
		S Sobel	
		S Brennan	
B22364	17	Fri, Nov 01, 1996	Minor Amendment Revised FOI Environmental Assessment
		S Sobel	
		S Brennan	
B22364	18	Tue, Nov 05, 1996	Pending New Drug Submission
		S Sobel	
		I Martin	
B22364	19	Wed, Nov 06, 1996	Minor Draft Labeling Amendment (Immediate Container Labels)
		S. Sobel	
		I. Martin	
B22645	20	Fri, Nov 15, 1996	Drug Interaction Study
		S. Sobel	
		I. Martin	
B22645	21	Fri, Nov 15, 1996	Draft Briefing Document
		S. Sobel	
		I. Martin	
B22645		Mon, Nov 25, 1996	Briefing Document
		K Reedy	
		I Martin	
B22645	22	Tue, Nov 26, 1996	Additional Safety Information
		S Sobel	
		I Martin	
B22680	23	Wed, Dec 04, 1996	Request for Information
		S Sobel	
		I Martin	
B22687	24	Thu, Dec 05, 1996	Request for Information
		S Sobel	
		I Martin	
B22687	0	Thu, Dec 05, 1996	Desk Copy: Response to FDA Request for Information
		R Misbin	
		I Martin	

SubType: NDA

CI#: 991 | Sub Date: 7/31/96

Generic:

Appr Date:

Product Name: Troglitazone

Barcode	Ser/ Ref#	Date	To: / From:	RE/ Contents/Report No. / Report Title/ Report No.
	25	Fri, Dec 13, 1996	S Sobel I Martin	Response to Request for Information